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# The Relationship of Certain Focal Infections to General Disease in Infants and Young Children \*

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**D**URING recent years, much evidence has accumulated to emphasize the importance of focal infections in the causation of general disease during infancy and childhood. We have gradually come to realize that certain conditions, which previously have been regarded as nutritional and metabolic in origin, are in reality the result of infection. Certain infections such as those in tonsils and adenoids, middle ear, chest, genito-urinary system, bones and skin, can usually be recognized without much difficulty, by anyone who conducts a systematic search. There are other locations, however, in which infections occur which are not so obvious: for example in the mastoid antra of infants and in the nasal accessory sinuses of infants and young children. Failure to recognize these infections or properly to appraise their importance has been due to the difficulties of examination, the frequent absence of local symptoms and the prevalent but erroneous belief that the mastoid cells of infants

and the nasal accessory sinuses of young children are not sufficiently well developed to be the seat of infections or to be amenable to treatment.

The general effects of infection are largely dependent upon the nature of the infecting organism. Thus infections in the mastoid and nasal accessory sinuses may lead to such a variety of conditions as vomiting, diarrhea and failure to gain in weight in the case of infants; hemorrhagic and tubular nephritis, heart disease, chorea, malnutrition, asthma and cyclic vomiting in older children. The clinical picture of low grade sinus infection may simulate that of such widely different conditions as pulmonary tuberculosis, appendicitis, malaria or encephalitis. There is no group of conditions in which the diagnosis is more frequently missed or in which treatment is more satisfactory, once a correct diagnosis is established, than those in which the infections mentioned are responsible.

The pediatrician sees these conditions at their onset and it is his responsibility to make the diagnosis and see that such treatment is carried out as will prevent chronic disease in later life. Even during earliest infancy focal infections may occur which

(\*From the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital.

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cause systemic manifestations. We have encountered mastoid antrum infections in premature infants during the first few weeks of life, and definite sinus infections in infants during the first four months of life.

During infancy the chief problem of the pediatrician is that of nutrition. We now have a clear idea as to the nutritional requirements and digestive capacity of the infant and have learned that all of the requirements may be readily met by simple foods and, most important of all, we have learned that if an infant has been taking a suitable food in adequate amounts and is failing to thrive, or has developed vomiting and diarrhea, the food is not at fault and does not need to be changed. The essential thing is to determine the underlying cause of the symptoms and this will most likely be found to be infection, either within or without the gastro-intestinal tract, provided, of course, that anomalies or mechanical conditions such as congenital malformation of the heart, or pyloric or intestinal stenosis are excluded. Congenital anomalies are rare and usually recognized without difficulty. The infections must be sought out.

Infection occurring within the gastro-intestinal tract itself may be the cause of the difficulty as in the case of bacillary dysentery and such infections should be discovered and appropriately treated or else ruled out. It is equally important to seek for such parenteral infections as we know are likely to be etiological factors in bringing about gastro-intestinal and nutritional disturbances. Infections of the middle ear are most common during early infancy. In most instances otitis media

is readily recognized if one carefully examines the tympanic membrane. In other instances it is not so easy, particularly in the case of malnourished infants who have failed to thrive for a long time. The drum membrane may be neither red nor bulging, but careful observation with the electric otoscope may reveal a lack of luster and transparency. Paracentesis in such a case may be followed by the discharge of only a small amount of serum or a larger amount of pus. In a certain number of instances paracentesis is followed by improvement in the infant's general condition irrespective of any change in the character of the diet. Such happy results are, however, not always obtained. Severe diarrhea may continue or the infant may fail to thrive. In these cases, after other sources of infection have been searched for and ruled out, one should consider a possible infection of the mastoid antrum. Such infections are much more common than has been previously realized.

During early infancy the antrum and middle ear form essentially one cavity, communicating through the narrow *aditus ad antrum*. The antrum is the only mastoid cell developed at an early age and is a small cavity no larger than a pea. In middle ear infections the antrum is probably involved in most instances. When the middle ear is drained the antrum also drains unless obstruction occurs at the *aditus*. Such obstruction is not uncommon in infancy, as the *aditus* is narrow and the mucosa readily swells so as to completely shut off the antrum from the tympanic cavity. In these instances the infection remains in the

antrum and gives rise to constitutional manifestations. A walled-off infection in the antrum in the majority of instances does not lead to any local evidences over the mastoid region. There may be no redness, edema or apparent tenderness. The only local sign may be a sagging of the posterior superior canal wall just external to the tympanic membrane. This sag is due to the fact that the bony annulus is not complete so that pressure from within the antrum causes a protrusion of the canal wall. At times the sag may be so slight as to be hardly discernible. It is, in most instances, not recognized unless one is particularly looking for it and is using the electric otoscope.

The decision to drain the antrum rests on the pediatric as well as otologic considerations. The general symptoms depend to a certain extent upon the nature of the infecting organism and are not proportional to the degree of temperature reaction. We have observed epidemics of mastoiditis in infants, due to certain strains of hemolytic streptococcus, in which the symptoms were of a fairly uniform type and consisted of fever, diarrhea of the cholera infantum type, associated with dehydration and hydrolability, whereas other infants with mastoid infection of equal severity and, at times, with higher temperature showed neither vomiting nor diarrhea when the infecting organism was of a different type. The streptococcus, however, is not the only organism capable of bringing about severe diarrhea, although it is perhaps the most important. Members of the colon group and certain types of pneumococcus as

well as other organisms have, in individual cases, led to severe diarrhea. On the other hand, there are strains of streptococci as well as other organisms which, when present in the mastoid antrum, lead to no very violent symptoms, but only to a slow but progressive loss in weight, occasional vomiting and ultimately to a condition of athrepsia or marasmus. In these cases there may be little or no fever but the blood leucocyte count is invariably elevated. Infections of the mastoid antrum which are acute in nature and lead to definite subperiosteal swelling rarely lead to the constitutional manifestations mentioned above and recovery in this latter group after operation is usually prompt.

When no other explanation for the symptoms is present and especially if there are otological evidences of antrum infection, the antrum should be drained. The operation, as performed in our clinic, has been described by Alden and Lyman (1). Local anesthesia only is used and a small button of bone over the antrum is removed and a gauze wick inserted. There is no appreciable shock and, in our experience, no mortality referable to the operation *per se*. We refer to this simple operation as "post-auricular drainage" or "antrotomy" rather than mastoidectomy. In most instances it is advisable to do post-auricular drainage on both sides, for bilateral infection is the rule. This simple operation has, in our experience, given most gratifying results, especially when done early and before the infant is in critical condition. Many of our worst cases of diarrhea, vomiting and severe nutritional disturbances

have responded promptly with marked improvement and ultimate recovery. It has been our custom to make no changes in the character of the feeding in these cases.

To give some idea of the frequency of these infections, there were recently 32 infants under two years of age in the wards of the St. Louis Children's Hospital; of these 28 had had antrotomies, and in each instance definite infection in the mastoid antrum was discovered at the time of operation. It is during infancy that walled off mastoid antrum infections are especially likely to occur because of the anatomical considerations already mentioned.

As far back as 1684 Du Verney (2) recognized the presence of pus in the mastoid antra of young infants. It has been generally recognized for a number of years that nutritional and gastro-intestinal disturbances during infancy may be the result of infections in the middle ear. This point of view was clearly expressed by Hartmann (3) in 1898. Maurice Renaud (4) seems to have been one of the first observers to attribute nutritional disturbances in infants to infections of the mastoid antrum. Renaud based his conclusions on autopsy findings and on the beneficial effects of antrotomy. Byfield (5) and Floyd (6) working in conjunction with Dean of Iowa City have reported on cases of masked mastoiditis in early infancy in which excellent results were obtained following operation. Our own work on this subject was begun in 1923 when we discovered mastoid antrum infections at autopsy in the case of infants dying from severe nutritional disturbances.

Following this finding a number of mastoid antra were opened during life and found to be infected and there was subsequent improvement in the general condition of the infants.

Certain nasal accessory sinuses are present, although small, even in early infancy. The maxillary antra are present, membranous sphenoids and some of the ethmoid cells. As the child grows, all of the sinuses enlarge and the frontal sinuses are ultimately developed. Sinus infection can occur at any age, and give rise to general symptoms. The diagnosis is difficult but possible even on very young children.

Direct rhinoscopic examination with a proper light is the surest method of detecting the local condition. In some instances it is advisable to conduct the examination under anesthesia with the use of the naso-pharyngoscope. The observation of pus coming from any of the sinuses of course makes the diagnosis evident, but it should be emphasized that the visualization of free pus is not essential for the diagnosis of chronic sinus infection. There may be merely reddening and swelling around the ostia or a slight serous exudate. In the case of maxillary sinusitis, the diagnosis may be confirmed by irrigation and culture of the material removed. Local symptoms of pain and nasal discharge are not necessarily present, but enlargement of the cervical glands, especially of the posterior chains is a constant finding.

Transillumination of the sinuses is of relatively little value as a means of diagnosis. The X-ray is of much greater value but this, too, is at times

untrustworthy. Lack of development of one or more sinuses, particularly of the frontals as revealed by roentgenography is indicative of long standing infection.

One of the most frequent general manifestations of chronic sinus infection in children is a picture simulating that of tuberculosis. The child is pale, languid, has slight evening temperature and often a chronic cough. X-ray of the chest in these cases shows an enlarged hilus shadow and peribronchial thickening, often extending well out into the parenchyma of both lungs. Small dense areas such as are usually interpreted as shadows of calcified glands may be seen. Tuberculosis in these cases may be ruled out by negative intradermal tuberculin tests using increasing amounts of tuberculin. Successful treatment of paranasal sinus infection in these cases results in marked and progressive improvement.

Other symptoms which we have often observed associated with chronic sinus infection have been repeated attacks of abdominal pain, often accompanied by vomiting. In some of these patients the symptoms have been so suggestive of appendicitis that the abdomen has been opened but no pathological conditions found, except in certain instances enlarged abdominal glands. Brenneman (7) has drawn attention to the association of such abdominal attacks with throat infections. Chronic digestive disturbance associated with achlorhydria is another manifestation of chronic sinus infection.

Asthmatic symptoms are observed in children suffering from chronic sinus infections. When asthma is due

to definite sensitization, there occurs a hypertrophic condition of the nasal mucosa which is said to predispose to sinus infection. In other instances, however, the sinus infection is apparently the original cause of the asthma.

Children with chronic sinus infections, especially those who are also malnourished, are likely to develop heart murmurs and a certain degree of cardiac dilatation. The erroneous diagnosis of organic heart disease is often made on these patients, but the disappearance of the murmurs and the return of the heart to normal size following the removal of the infection and improvement of the general nutrition speak against the probability of valvular endocarditis. On the other hand, sinus infection is usually observed in patients having true rheumatic endocarditis and the other rheumatic manifestations of chorea and articular rheumatism. In this rheumatic group the sinus infections have not usually been accompanied by the presence of thick pus, but there has been a thin serous pus found in the sinuses, especially the maxillary antra and in addition in those cases which have been operated upon radically a tremendous amount of granulation tissue has been found. In our experience, clearing up of sinus infections has been more effective in preventing recurrence of chorea, rheumatism or endocarditis than has the mere removal of tonsils and adenoids.

The association of chronic arthritis with focal infections is, of course, well recognized.

One of the most important and clear cut of the manifestations of infection in the nose and throat is ne-

phritis. The two common forms of nephritis occurring in childhood, namely tubular nephritis or "nephrosis" and glomerular or "hemorrhagic" nephritis have, in our experience, invariably been associated with infection. The infection has been found more frequently in the nose and throat than elsewhere in the body. The characteristics of tubular nephritis or nephrosis are the passage of scanty amounts of urine containing large amounts of albumin and numerous casts but no blood, normal phenol-sulphonephthalein output, no retention of non-protein nitrogen and no elevation in blood pressure; marked generalized edema and ascites and severe anemia. Clausen, (8) working on cases of nephrosis in the St. Louis Children's Hospital, pointed out the association of these cases with infections of the paranasal sinuses, especially the maxillary antra. The infecting organism has most frequently been a hemolytic staphylococcus. Clausen (9) demonstrated the presence in the blood and urine of a substance having a marked physico-chemical effect and capable of altering the permeability of membranes. This substance disappears from the blood and urine coincident with a clearing up of the sinus infection and subsequent disappearance of the edema. The effect of suitable treatment has been truly remarkable in these cases of nephrosis. Thus we have observed a young child to lose as much as 15 pounds of fluid within five days time, following the drainage of infected sinuses. When the sinus infections have been satisfactorily cleared up, complete disappearance of the albumin from the urine is

the rule. We have examined a number of these patients at intervals for several years afterwards and have found no remaining evidence of nephritis. Re-infection of the sinuses may, however, cause a return of all the symptoms. Infections which have persisted for a long while sometimes lead to permanent changes in the kidneys, but complete recovery is possible in the case of uncomplicated tubular nephritis. Unfortunately it is not always possible to completely eradicate the infection but this is the only method of treatment which is calculated to bring about more than temporary or symptomatic improvement. Dietary regulation, restriction of fluid, sweating, purging and the use of diuretics are methods of treatment capable of accomplishing no permanent improvement. Recovery following the use of such methods is to be attributed to spontaneous clearing up of the infection in the sinuses or elsewhere.

Hemorrhagic or glomerular nephritis is usually, if not always, the result of a streptococcus infection. The most common causes of such a nephritis are streptococcus infections of the nose and throat, including the scarlatinal infections. The streptococcus is more likely to invade the tonsils, adenoids, middle ears and mastoid than the nasal accessory sinuses. In glomerular nephritis, in distinction to nephrosis, there is blood in the urine at some stage, the urine is not necessarily scanty, retention of non-protein nitrogen occurs in the blood and in cases of long standing some degree of hypertension is the rule. There are also changes in the capillaries throughout the body. In the majority of in-

stances, hemorrhagic nephritis is of short duration and clears spontaneously. If, however, the infection persists for a considerable length of time permanent damage to the capillaries of the renal glomeruli occurs and then, even though the source of infection is subsequently removed, complete recovery is not possible.

The conditions so far mentioned are those of fairly common occurrence. Occasionally certain bizarre symptoms referable to sinus infection are observed. Thus we have seen three patients whose symptoms simulated epidemic encephalitis. We have observed in different patients hemiplegia, paraplegia and a symptom complex referable to extra-pyramidal lesions in which the association with sinus infection was definitely established. We have also observed children whose symptoms were indistinguishable from idiopathic epilepsy in whom the manifestations have ceased following the successful treatment of sinus infection.

The diagnosis of sinus infections in general must be made by the internist or pediatrician rather than by the otolaryngologist. It is the internist who first sees the patient and unless he recognizes the general symptoms indicative of local infection, the otolaryngologist will not be called. The diagnosis of the individual sinuses involved is a problem for the otolaryngologist, but due to the fact that the importance of sinus infection in children has not until recently been sufficiently realized, consultations with otolaryngologists are often unsatisfactory. Infinite patience and special technic are necessary if a correct diag-

nosis is to be made and unfortunately otolaryngologists have centered their attention on tonsils, adenoids, and obvious mastoid infections to such an extent as to practically ignore the sinuses.

In the majority of instances local treatment, possibly with irrigation of the antra, is all that is necessary to bring about satisfactory results. The treatment as outlined by Arbuckle of this clinic has been most satisfactory. This consists in irrigation with a 10% solution of glucose (Cérellose) once or twice daily, followed by oil of rose sprays and the instillation of a weak mercurochrome solution of 0.3 to 0.5%. During the irrigation with the hypertonic glucose solution the head must be held forward and down. When the mercurochrome drops are instilled the child lies on the back with the head over the edge of the bed. Ephedrine instillations leading to a shrinkage of the nasal mucosa result in better drainage and tend to aid in bringing about a clearing of the infection.

In the presence of badly infected tonsils and adenoids, these should be removed. In some cases it is necessary to cut windows in the maxillary sinuses in order to bring about adequate drainage and ventilation.

In a few instances it becomes necessary to perform radical operations upon the upper nasal sinuses. In general, operation during the acute stage, especially of streptococcus infections, is to be avoided. The time for operation is during the subacute or chronic stage of the infection.

From what has been said, it must not be assumed that every infant with

vomiting and diarrhea or every child suffering from any of the manifestations mentioned should immediately be subjected to treatment operative or otherwise of the mastoid or nasal accessory sinuses. We do not wish to overemphasize the importance of these infections, but merely to draw attention to the fact that such infections are too often overlooked as possible factors in the causation of general symptoms. It is admitted that sinus

infections are frequent in children who show none of the symptoms mentioned and also that during almost any bad "cold in the head" there may occur some sinus infection. There is, however, a large group of cases in which an etiological relationship between sinus infection and general disease manifestations is so evident as to leave little doubt in the mind of the observer.

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# Mucous Colitis (Colonic Vagotonia)\*

By JOHN DUDLEY DUNHAM, A.B., M.D., *Columbus, Ohio*

THE synonyms by which this disease is known are numerous and confusing. Writers have used the terms: Myxorrhœa coli, muco-membranous colitis, myxoneurosis intestinalis membranacea, hypochondriasis pituitosa, catarrhal colitis, and chronic intestinal catarrh, most of which are misnomers.

The few necropsies (1) performed on patients dead of this disease when uncomplicated reveal no evidence of an inflammation of the large bowel.

Hence, colitis conveys a very erroneous conception. Cabot's (2) suggestion "colica mucosa" is better, though the part affected is not mentioned.

Colonic vagotonia covers the part involved as well as the etiologic factor.

The first description of this disease has a very ancient origin. It is to be found in II Chronicles, Chapter 21, verses 12-19 inclusive:

12 'And there came a writing to him (Jehoram), from Elijah, the prophet, saying, Thus saith the Lord God of David thy father, Because thou hast not walked in the ways of Jehoshaphat thy father, nor in the ways of Asa, king of Judah,

15 Thou shalt have great sickness by disease of thy bowels, until thy bowels fall out by reason of the sickness day by day.

18 And after all this the Lord smote him in his bowels with an incurable disease.

19 And it came to pass, that in process of time, after the end of two years, his bowels fell out by reason of his sickness, so he died of sore diseases.'

This was probably a case of mucous colitis. The powerful suggestion made through Elijah doubtless caused him to scrutinize his stools. Then arose the diarrhoea with mucous casts. The emotional state of the ancient king must have been distressing, causing his vagotonia and perhaps sitophobia and starvation. This patriarch was stricken at the early age of 38 and succumbed within 2 years. Had the Lord seen fit to revise his prophecy the altered emotional state of Jehoram might have released the hypertonicity of his vagus.

If our diagnosis is correct, the patient would then have been allowed to fulfill the allotted span of three score years and ten (3).

The scientific discussion dates at least to Paulus Aegineta in the early period of the seventh century, who considered the entity as a discharge of the inner coat of the bowel.

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## ETIOLOGY

Opinions about causation are as various as there are observers who have reported cases.

A preponderance of certain types of bacteria in the intestinal flora has been insisted upon by some clinicians as the sole factor.

Cabot (2) states that colica mucosa is a form of neurosis associated with constipation, recurrent attacks of diarrhoea and sometimes with starvation.

W. S. Thayer in a discussion of the above paper holds that "a nervous element is an associated element and is not the cause of mucous colitis."

Thus do the masters disagree.

Norman (4) contends that McCarrison's studies suggest a deficiency of Vitamin C with an excess of starches, or starches and fats, which produces pathologic lesions in the intestinal tract similar to those in mucous colitis. Further "mucous colitis must be considered as the most manifest part of a general constitutional disorder brought about chiefly through dietary deficiencies and excesses and the occurrence of other infections."

Goldman's (5) discussion of etiology holds that "the condition may be brought about by abnormal endocrine function, infection of the intestines from focal lesions in the teeth, tonsils, appendix, or gall bladder, from ptomaine or chemical poisoning, from mechanical obstruction, and from faulty metabolism."

J. M. Da Costa (6) was apparently the first to suggest the true conception of this disease as a dyscrasia of the vegetative nervous system. He said, "It is doubtful if we can consider the af-

fection as originally an inflammation at all. Is not the true trouble in the nervous system in the nerves presiding over secretion and nutrition in the abdominal viscera?

Chas. L. Mix (7) and B. L. Spitzig (8) have very clearly defined mucous colitis as a Vagotomy.

The effect produced upon the unstriped muscle of the alimentary tract through emotional states offers, to my mind, the only satisfactory explanation of mucous colitis. Worries, marital infelicities, unsatisfactory sexual relations all have a tendency to produce this disease.

Judge Lindsay's suggestion of companionate marriage would reduce the frequency of colonic vagotonia in young women.

No more classical or accurate clinical description of this disease has been written since Da Costa's article published fifty-five years ago. (6)

"The disease is characterized, as already said, by attacks of abdominal pain, followed by the discharge of what looks like skins or membranes, sometimes coming off in the shape of moulds or long tubes. There may be but one attack; but this is very exceptional, much more generally one paroxysm is followed after an interval of months by another, and yet another; and at times the disease may become almost continuous, with occasional distinct exacerbations. A week, in my experience, is the shortest time for an attack to last, and distention, sense of burning, colicky pains and at times a sluggish state of the bowels, precede the discharge by days. After this has taken place, the abdominal soreness lessens, the feeling of raw-

ness passes off, and the patient is well, though he is apt to have a coated, flabby tongue, to remain dyspeptic, and be readily fatigued. If he has lost flesh during the seizure, he regains it entirely, or to a great extent, and, at no time, unless in an aggravated case, does he emaciate much. From the history of the ailment and the amount of abdominal soreness during the attack, we might expect febrile phenomena, but the skin is prone to be cool, the hands and feet are often moist and clammy, and the circulation feeble and languid. Palpitation, particularly of the abdominal aorta, is common. Between the attacks, the bowels are irregular, sometimes constipated, at others loose; and tenesmus is often complained of. The patient suffers from sore mouth, from papular eruptions, from boils, or even carbuncles; he has an unhealthy complexion, and *almost invariably exhibits some signs of his nervous system being disordered*. His bladder sympathizes in the intestinal derangement; it is irritable, and we have not unfrequently observed that large quantities of mucus are passed. All these symptoms come out in bold relief, during an attack, but in a slight form they may be noticed in the interval. After a few seizures the patient may gradually recover, yet is never robust, or the disorder becomes persistent. I repeat that in the rarest of instances only is it a short one."

#### DIAGNOSIS

Patients usually consult a physician with the diagnosis ready made in a specimen bottle. The tendency to in-

tropection and constant observation of the stool is almost universal.

To avoid error the stool should be carefully examined to eliminate particles of food, intestinal parasites and the evidences of actual colitis with ulceration.

If you find blood in the stool you are not dealing with colonic vagotonia.

The physician may be misled by the character of the pain and soreness into a diagnosis of peptic ulcer, cholecystitis, or appendicitis.

Operations upon patients with mucous colitis are much less frequent than in former years.

Surgeons have learned to be very sceptical about diagnoses of supposed abdominal lesions when patients have psychasthenia or hypochondriasis.

Every patient in whom there is a suspicion of colonic vagotonia should have a sigmoidoscopy performed as well as a fluoroscopic observation, of a barium meal. The latter procedure will reveal the phenomenon of spasticity which is an essential occurrence.

Mild cases without colic are most frequently overlooked and treated for hyperchlorhydria, neurasthenia, etc.

Thoughtful clinicians realize the wide spread occurrence of this type of disease.

#### TREATMENT

A perusal of the literature in recent years presents the most varied suggestions from capable internists.

One finds the extremes of a roughage diet and a very bland diet recommended. Some insist upon repeated colonic irrigations, apparently to free the bowel of mucus, while others advise against any local interference with the gut.

Luginbuhl (9) very aptly remarks that "colitis is no exception to the general rule that treatment should be directed to the cause, rather than to the suppression of the effect."

With many others he strongly disapproves of irritant cathartics and copious flushings of the bowel.

A bland non-irritating, nourishing diet has an appeal as a rational procedure in these cases. If the patient can add 10 or 20 pounds to his weight improvement is aided.

If one accepts the well established theory that true mucous colitis is caused by a disturbance of the emotions with a resultant hypertonicity there should be no question as to treatment.

A careful analysis of the patient's mental state and psychic shocks is fundamental.

This usually cannot be determined at one consultation and often only after a protracted period in which the confidence of the patient is secured.

Personally, I have never seen this disease in other than psychoneurosthenics or hypochondriacal individuals.

After the nature of the abnormal emotional state is discovered, the phy-

sician must use suggestion and also attempt to change the patient's attitude toward his life.

Re-education for the purpose of drawing his attention away from the bodily functions is a *sine qua non*.

This can never be done by drugs, colonic irrigations, or close attention to diet. Belladonna is the only drug which I have found beneficial. The more rectal injections the longer you will treat the patient.

Those who have recognized many cases of colonic vagotonia will realize that the treatment is not along a flowery path.

Unless the patient can be made to understand that he has no serious organic disease and that his disorder is curable largely by his own efforts, your psychotherapy will be unavailing.

Without the above management of your patient, autogenous vaccines, colonic irrigations, drugs, cathartics, and even implantation of *B. Acidophilus* will not cure the disease. Improvement by these latter means must be explained upon the theory of suggestion.

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# Treatment of Carcinoma of Rectum by Radium\*

(Presentation of Case)

By T. E. JONES, M.D., *Cleveland Clinic, Cleveland, Ohio*

WHILE we feel at the present time that whenever possible the best treatment for cancer of the rectum is some type of radical operation, there remain two classes of patients to whom we must offer some alternative treatment: first, those who are in an inoperable condition; and second, those who refuse the radical operation. There are a considerable number in the latter class who must command our attention, for if we do not offer another therapeutic measure they will immediately become the prey of quacks. We have therefore resorted to the use of radium in the treatment of these two classes of cases and wish to report our results in a series of 65 cases.

Radium has certainly established its value in the treatment of epithelioma of the skin, lip and tongue and of cancer of the antrum and cervix, but its use has been more limited in the rectum, and we shall have to have more statistical information and better results than have been obtained in the past before this field will be yielded to radiation therapy, as has happened in the case of can-

cer of the cervix. Although it is true that surgical results have not been excellent in the past, I believe that the surgical treatment of cancer of the rectum will improve in the future and will show a greater percentage of cures, so that radiation therapy will also have to advance in order to compete with surgery.

With the possible exception of cancer of the esophagus, cancer of the rectum is one of the most difficult diseases to treat successfully, chiefly because of its inaccessibility. Most malignancies are quite easy of access, at least as compared with cancer of the rectum. I would also call your attention to the difficulty encountered in the treatment of cancer of any organ which is physiologically functioning for the well-being of the patient, such as the esophagus, the stomach, the bladder, or the rectum. In the treatment of other organs such as the uterus, on the other hand, there is no particular physiological function to be provided for, the radium can be applied more easily, the dose can be larger, and all of these factors aid in securing better results.

In the treatment of cancer of the

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rectum we advise a colostomy preliminary to the radium treatment—the incision being made large enough to permit an exploration for the purpose of determining the condition of the liver, the mesenteric glands, and the peritoneum in the floor of the pelvis, for obviously if these are grossly involved the patient should not be subjected to treatment which will not benefit him. Colostomy greatly minimizes the discomfort of the patient during the period of reaction to the radium treatment, and while in the past some cases have been treated without colostomy, at the present time we insist on it.

After the colostomy has been made the distal segment of the colon is irrigated daily with large quantities of water to insure absolute cleanliness, for in the presence of infection the reaction to the radium is likely to be quite severe. The radium treatment is given about seven days after the colostomy has begun to function satisfactorily.

The technique of the application of radium differs somewhat with the nature of the lesion. If it is papillary in nature, needles or emanation tubes may be placed throughout the growth. If there is a large flat ulceration, an oval flat applicator can be made with radium tubes evenly distributed throughout. If there is a narrow constriction, tubes can be placed in tandem in a rubber tube and directed into the lumen of the bowel. It is very essential that the radium be placed accurately in proximity to the

growth and we recommend that the procedure be carried out under sacral anesthesia without moving the patient from his bed. If one gives a general anesthetic or moves the patient after treatment the radium is quite likely to be displaced.

The dosage varies with the size of the growth. In our cases the dosage has varied from two to three thousand mg. hours, the average being 2600 mg. hours. Two treatments are generally given about three hours apart. In one case, however, in which a papillary growth had extended to the buttock and vagina, over five thousand milligram hours were used. We employ a  $1\frac{1}{2}$  mm. brass screen the thickness of a rubber tube, which is about 3 mm. When the radium reaction has subsided the patients are given external radiation by x-ray. According to our experience, further radiation after the initial course is of little value. If recurrence takes place it is treated by the implantation of a few seeds in the area, but a large amount of radium is not needed and should not be used, for it is quite apt to produce excessive pain. If after one and one-half or two years there is no evidence of disease, and the bowel is not constricted, then if the patient insists, the colostomy may be closed. This has been done in two of our cases.

*Complications:* The chief immediate complication of treatment with radium is pain and a bearing-down sensation and these, if severe, combined with loss of sleep wear out the patient very quickly. These symptoms are due to the intense in-

inflammatory reaction and generally begin about 10 days after the radium has been applied. The amount of the discomfort is generally proportionate to the area of normal mucous membrane which has been affected, so that it is necessary to protect this as much as possible, and therefore whenever it is possible, I insert a lead plaque 2 mm. thick between the radium tubes and the healthy mucosa. Olive oil enemas and suppositories are of some help in relieving the discomfort. Often in about three or four weeks after the treatment these patients complain bitterly of hemorrhoids. This is due to thrombosis in the hemorrhoidal veins and the ensuing congestion lower down. If there is thrombosis of the external veins it can be relieved by turning out the clot.

In all cases in which a colostomy has been made through and through irrigation is carried out, for cleanliness is of great aid. The closer the growth is to the sphincter the more severe the pain, therefore in such cases I perform a subcutaneous myotomy on the sphincter ani, using much the same technic as is used in making a subcutaneous tenotomy. This greatly relieves the terrific spasms of pain. The advantage of making the myotomy subcutaneously about an inch from the anus is that no raw surface is left at the muco-cutaneous junction, which in itself would be painful on account of the irritating discharge, and might heal with difficulty.

The later complications that appear are stricture of the rectum and metastases. We know that in the

healing process a great deal of scar tissue is produced, which later contracts and often almost completely obliterates the lumen, but this is not necessarily serious if we have been fortunate enough to eradicate the disease. It does, however, complicate the closure of the colostomy. We have several cases in which the colostomy could be closed except for this complication. I am contemplating trying out the carbon dioxid snow treatment for these strictures, but whether or not this would have the same effect as in benign strictures I am unable as yet to say.

Metastasis into the pelvic glands is generally evidenced by pain deep in the pelvis and hip and referred down the leg. When this occurs further x-ray treatment may be tried but radium is not advised. If the primary growth was in the distal inch and a half of the rectum, such extension is by the inguinal glands; and if they are present it is well worth while to remove them surgically. Extension into the liver occurs frequently and occasionally into the lungs, and for carcinoma in these organs treatment so far has not been successful.

*Results:* In our series of 65 cases of carcinoma of the rectum a colostomy was performed in 53; the other 12 patients refused to have a colostomy, and of these all except one are dead.

Approximately two-thirds—44—were in men and one-third—21—were in women. The average age of the men was 57, of the women 45. Thirty-nine of the men were

married and six single; 16 of the women were married and five single. The oldest patient in this series was a man, 74 years of age, the youngest a woman 25 years of age. An interesting feature of this series is the wide variation in the duration of symptoms before the patients came to us—these periods varying from one to 36 months, the average period being 12 months. A mistaken diagnosis, frequently of hemorrhoids, was usually the cause of this delay. We feel that these mistaken diagnoses are usually to be attributed to the custom of making a diagnosis without a digital examination.

That so many of these patients could go along for 36 months without serious difficulty can only be explained by the fact that cancer is variable in its attack on different individuals. One cannot base a prognosis on information gained from mass statistics, for no two cases behave the same. This point is well illustrated by one of our cases of carcinoma of the cervix, in which the patient had had the growth for 11 years and had received no treatment. Before we examined her we were reluctant to believe that the growth could be a cancer, but the diagnosis was confirmed by a microscopic examination. In some cases patients with cancer of the breast also remain untreated for many years without any ill result. In like manner the course of rectal carcinoma varies with the individual.

the 65 cases in our series 57 were inoperable and eight were

operable. Of the eight operable cases, six patients are living and two are dead; and among the six who are living the duration of life to the present time has been from two to four years. Of the 57 inoperable cases, eight of the patients are living and 49 are dead; among the eight patients who are living, the duration of life has been from two to four years. The average duration of life among these eight living patients has been 35 months, and they have all been able to resume their regular occupations.

One case in this series deserves particular mention:—The patient was a man 68 years of age when he first came to us, four years ago. At that time he had a carcinoma of the lower portion of the rectum, near the sphincter. A colostomy was done on February 27, 1923, and radium was applied one week later. The lesion healed very well and at the end of 15 months the colostomy was closed. In March, 1925, 25 months after the primary lesion was treated, a metastasis developed in the left inguinal glands. The glands were excised on both sides and ten days later the right and left inguinal regions were treated by x-ray. The excision was followed by transient elephantiasis of the penis and the scrotum but there have been no other ill effects. It is now two years since the inguinal glands were removed and over four years since the carcinoma of the rectum was treated, and the patient is perfectly well. Cases such as this prove that one cannot foretell what the results of treatment may be.

# General Discussion of Diseases of the Spleen\*

By JOHN TUCKER, M.D., *Cleveland Clinic, Cleveland, Ohio*

**B**EFORE entering upon a discussion of certain pathological conditions of the body which are produced wholly or in part by abnormal changes in the spleen we must consider certain aspects of the anatomy and physiology of this organ. The large size of both the splenic artery and vein demonstrates that this organ is important as a hematopoietic or hemolytic structure. It has been asserted that at birth about 20 per cent of the portal blood comes from the spleen and in disease even a larger percentage of the hemo-fluid originates in this organ. As to its internal structure, we are particularly concerned with those large endothelioid cells which are present in the reticulum and pulp and which histologically have the power to take a vital stain. These great cells with single nuclei and clear cytoplasm are found not only in the spleen itself but also in the lymph nodes, in the adrenal cortex, in the hypophysis, as the Kupfer cells of the liver, as the Rouget cells of the capillaries and bone marrow, and as the endothelial cells of the body.

These characteristic cells, which

are scattered so widely through the body, have been termed by Aschoff (1) the *reticulo-endothelial system*. To them have been ascribed many functions which formerly were thought to be limited to the spleen. Therefore we would like to discuss the normal and pathological functions of the spleen not only as an organ *sui generis*, but as a member of this important and widespread system — the reticulo-endothelial system of Aschoff.

The many functions of the spleen which are known or which are supposed to exist are as follows:

I. The spleen is a reservoir for the red blood cells in the body. Reasonable proof of this storage function has been adduced by Prof. J. Barcroft (2). He shows by experiment that splenectomized guinea pigs die sooner in an atmosphere of pure coal gas than do guinea pigs with intact spleens. His explanation of this phenomenon is that when the red blood cells of the circulating blood are so saturated with carbon monoxid hemoglobin as seriously to impair the ability of the blood to supply oxygen to the tissues, then by its maximal contraction the spleen forces a quantity of normal red blood cells into the blood stream. Thus by giving a temporary fresh supply of oxy-

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hemoglobin to a splenectomized animal its life will be prolonged for a short time.

II. A second function indicated by the above experiment is that the spleen has the ability to expand and to contract—thus assisting in regulating the total volume of blood. By a second ingenious experiment Prof. Barcroft and his associates proved this point. He attached lead strips to different points in the splenic surface in cats and then by taking x-ray plates he demonstrated that the spleen varies greatly both in shape and size during different phases of digestion, and its size is reduced by exercise. He proved also that after the death of the animal the spleen may be only one-half the size of the resting spleen during life. If we are justified in applying these findings in animals to man, then we must admit that the spleen 'pulsates' and we must also recognize that in the living human subject its weight is more than that of the average spleen in the cadaver—195 gms. That is, during or shortly after the period of lethal exodus the size of the spleen is reduced by contraction.

III. The spleen increases the fragility of the red blood cells in the presence of hemolytic agents. Many workers have shown that the red cells of the splenic vein are less resistant to hypotonic salt solutions than are the red cells of the peripheral circulation. In 1918 Drs. Pearce, Krumbhaar and Frazier (3) concluded an important study on the effect of splenectomy in dogs. One of the facts established by these investiga-

tors was that after splenectomy the red blood cells show increased resistance to hemolytic substances such as hypotonic salt solutions, hemolytic serum, saponin, venom and mechanical agitation. In the presence of certain pathological changes in the spleen and reticulo-endothelial system—as in Banti's disease and familial hemolytic icterus, we have every reason to believe that this function of blood destruction is increased to pathological proportions with the resultant production of anemia and the overloading of the liver with bile pigments and toxic products of cellular degeneration by way of the splenic vein, these sequelae progressing to the ultimate production of jaundice and hepatic cirrhosis.

IV. As a corollary to the function of red blood cell destruction Mann and Sheard (4) of the Mayo Clinic have performed experiments which give certain evidence that the reticulo-endothelial cells of the spleen and elsewhere are able to form bile pigment from the iron-free moiety of hemoglobin, thus forming at least a part of the liver bile. During my own term as House Officer at Lakeside Hospital I was able to show that bile pigment could be formed from blood extravasated into various serous cavities of the body. This included the pleura, peritoneum, pericardium, subarachnoid space and synovial sacs of the knee. Whipple (5), also, has long since shown that bile pigment can be formed outside the liver.

V. A fifth function of the spleen is its ability to destroy blood platelets. The fact is now generally accepted that the presence of a sufficient number of blood platelets is essential to the formation of a normal *retractile* clot, and that if the platelets are insufficient in number or are absent, then the clot, even though it forms in a normal period of time, will nevertheless be non-retractile, so that there is resultant predisposition to hemorrhage.

In this discussion I wish to call your especial attention to three of these functions which may reach harmful proportions when the spleen and reticulo-endothelial system are diseased—viz. the destruction of red blood cells, the destruction of blood platelets, and the sending of abnormal quantities of bile pigment and toxic products to the liver.

To illustrate these changes, I should like to discuss three types of diseases of the spleen and of the reticulo-endothelial system:—(1) Splenic anemia or Banti's disease; (2) hereditary splenomegalic hemolytic jaundice; and (3) thrombocytopenic purpura hemorrhagica. Each of these conditions represents a disturbance of one or more of the above functions of the reticulo-endothelial system.

*Banti's disease*—splenic anemia—is characterized by a progressive enlargement of the spleen, secondary anemia usually intermittent, a tendency to hemorrhages, especially those of gastric origin, esophageal varices, and later secondary cirrhosis of the liver with jaundice and ascites (Osler). Leucopenia is

usually present. The disease is often divided into three periods: (a) enlargement of the spleen, (b) beginning congestion of the portal circulation, (c) cirrhosis with ascites. Pathologically there is marked fibrosis of the spleen with increased firmness in its texture and thickening of the capsule. Banti has found a proliferation of the endothelial cells of the venous sinuses of the pulp. This would correspond to the hyperplasia of the reticulo-endothelial system demonstrated by Aschoff.

Splenectomy gives the best results in the first stage, although cases of cure have been reported even after cirrhosis of the liver and ascites have developed.

It is very unusual for this disease to be seen in children. However, two of our cases were in children, one in a boy of 6 years and another in a boy of 7 years of age. Both had anemia, an enlarged spleen, gastric hemorrhages and leukopenia, but no cirrhosis or ascites. Both of these patients made a good recovery after splenectomy. Both children are living more than three years since the operation and while they are not robust they are in reasonably good health; the blood counts are over 4 million and there has been no recurrence of hemorrhages.

In a third case—that of a boy 19 years—the usual picture of splenic anemia was present. This patient made an exceptionally good recovery after splenectomy. His disease must have existed for fully 15 years, since he had had an en-

larged spleen and had vomited blood at the age of 4 years. Prior to operation an examination of his blood gave the following findings:—R. B. C., 1,650,000, W. B. C., 1300 and Hb., 30 per cent. A blood transfusion with splenectomy raised the cell count to R. B. C., 6,400,000, W. B. C., 17,800 and Hb., 75 per cent. While this patient was in the hospital a severe attack of streptococcic tonsillitis developed and the white blood cell count rose to 25,000, but he seemed to resist the infection very well and the acute phase of the tonsillitis subsided. Since that time he has had two recurrences of tonsillar inflammation but has resisted the infection very well with no material diminution in the red blood cells. The tonsils are still enlarged and there is a large lymph gland in the upper anterior triangle of the neck on either side. The patient's mother has repeatedly refused to permit a tonsillectomy—"So long as Bob is doing so well, I do not want him to risk another operation."

This last case brings out two interesting points:—(a) that the patient was able to tolerate splenic anemia for at least 15 years without the development of demonstrable cirrhosis of the liver and ascites; and (b) that he has been able to resist three attacks of tonsillitis and to carry septic tonsils without a recurrence of the anemia. This case together with several others in which infection has appeared in patients after removal of the spleen leads me to believe that splenectomy does not cause any lowering

of resistance to infection. Certainly we are quite sure that after removal of the spleen the other portions of the reticulo-endothelial system undergo hyperplasia and if antibody formation occurs in this system then the patient is in better condition to resist infection after the diseased spleen is removed.

II. *Hereditary splenomegalic hemolytic jaundice*, first described by Munkowsky, presents a problem somewhat different from that presented by Banti's disease. The main characteristics of this syndrome are as follows:

The disease dates either from birth or begins in infancy or in early adolescence. The patient is continuously jaundiced but apparently is not ill. There is a chlorotic type of anemia—that is, there is a greater reduction in hemoglobin than in red blood corpuscles. The blood contains bile pigment but no salts and yet the urine is free from biliary elements. The presence of increased urobilin in the urine and stools indicates the abnormal blood destruction. The spleen is enlarged but the liver rarely extends much below the costal margin. The stools are normal in color. As a rule the red blood cells show increased fragility to hypotonic salt solutions. This condition may be hereditary but in such a case its course is similar to that of the acquired form. In the inherited type of the disease several members of the family are usually affected and the condition is probably handed down as a dominant Mendelian character.

Pathologically the spleen shows

marked engorgement and on microscopic examination the pulp seems to be crowded, while the sinuses are nearly empty. Gall-stones are present in about 60 per cent of the cases. There is a positive van den Bergh reaction from hemolytic icterus and the kidneys do not excrete the bile pigment.

The following case history will be cited in some details:

The patient, a little girl, 6 years of age, was presented with a questionable history of having had jaundice at birth. At the age of 2 years, however, the first frank appearance of jaundice occurred. Since then the skin had always been yellow with an underlying pallor. Exacerbations of the yellow color of the skin had been noted approximately every two months. The general health had been good save for a failure of appetite at the periods of icteric increase. There was no tendency to prolonged bleeding, no vomiting of blood, no nose-bleed and the urine had never been very dark in color. Occasionally the child had complained of a "hurting" in the stomach when awakening in the morning.

The *family history* was most important: the maternal grandmother, the great-grandfather, and an aunt had been habitually jaundiced. The mother also had been icteric and had had an enlarged spleen since childhood.

The *past history* of the patient included nothing of importance excepting a severe attack of measles in the preceding winter.

*Physical examination* gave normal findings except for a pale and

icteric skin, some puffiness of the face, and slight jaundice of the sclera. The spleen could be palpated  $4\frac{1}{2}$  cm. below the costal margin in the anterior-axillary line, it descended on inspiration and showed a sharply defined border but no palpable notch. There was no enlargement of the lymph glands except in the upper anterior triangle of the neck on either side.

*Laboratory tests* gave the following findings:—Secondary anemia; increase in serum bilirubin; no bile pigment in the urine; normal platelet count; negative Wassermann test; and increased fragility in the red blood cells.

In summing up this case we find hereditary jaundice, increased bilirubin in the blood but no bile in the urine; an increase in the fragility of the red blood corpuscles; normal blood platelets; and pathological findings which confirm the clinical diagnosis. There was a striking increase in the red blood corpuscles 10 days after the operation, which was a long enough period to discount the effect of the one transfusion performed at the time of operation.

III. *Thrombocytopenic purpura hemorrhagic* is the most interesting disease of the group of diseases of the spleen and reticulo-endothelial system. In the majority of cases of this disease the results of splenectomy are quite dramatic unless the disease is of too long standing, on the one hand, or of the acute fulminating type, on the other. The important points in the diagnosis are the following:—

(a) An enlarged spleen is usually present.

(b) Bleeding from any part of the body such as the stomach, nose, gums, uterus, kidneys; petechias and ecchymosis of the skin.

(c) Prolonged bleeding time, due to a non-retractile clot, although the clotting time is normal.

(d) Positive capillary pressure determined by test with tourniquet applied for 5 minutes, as first described by Hess of New York City.

(e) Marked diminution or absence of blood platelets known as thrombocytes.

When such a syndrome is present we can expect splenectomy will result in a cure unless the remaining portions of the reticulo-endothelial system continue the abnormal destruction of platelets. Various workers have shown that in thrombocytopenic purpura the blood platelets are destroyed by the splenectomy. By examining the arterial and venous blood of the spleen, Myers, Waingot and Gordon demonstrated in one case that the splenic artery platelets were 325,000 and splenic vein platelets 65,000, thus showing a marked diminution in the number of thrombocytes leaving the spleen.

Microscopically the spleen shows marked proliferation of the endothelium and of the pulp sinuses and the lumina are stuffed with large cells.

Even though the cure which follows splenectomy in these cases is usually very dramatic, yet one of our patients who presented a typical picture of this syndrome failed to recover.

This patient was a white woman,

33 years of age, in whom during an attack of influenza petechiae developed on the extremities. Subsequent to this she remained pale and had recurrent subcutaneous hemorrhages, profuse menstrual flowing, attacks of fever and gradually increasing anemia. No enlargement of the spleen could be discovered by physical examination. However, the platelet count varied between 17,000 and 155,000 (normal 200,000 to 300,000), there was a non-retractile clot, fragility tests gave normal findings and the red blood cell count varied between 1,216,000 and 3,260,000. We had hoped that a blood culture would show streptococcus but none was found. The abnormal blood platelet destruction gave definite evidence of disease of the reticulo-endothelial system. Even though the spleen could not be palpated clinically it was removed, but no benefit resulted. It was apparent that the spleen was playing only a minor part in the disease. After three months in the hospital the patient was allowed to go home. A month later she died, but unfortunately no autopsy was performed.

We feel sure that this case should be classed as one of thrombocytopenic purpura hemorrhagica and that it was initiated by a so-called "influenzal" infection. However, we could not find any focus of infection, blood cultures were sterile and splenectomy resulted in no improvement.

Among these three types of splenic disease hemolytic icterus appears to be the only one that may be hereditary, although in several of our cases of Banti's disease we have obtained a history of the appearance of pallor

and of an enlarged spleen very early in life. I believe that the thrombocytopenic purpura is the result of infection, probably streptococcic in type, with localization of the organisms largely in the splenic portion of the reticulo-endothelial system.

Due to the very short time at my disposal I have refrained from discussing other diseases in which splenectomy may be indicated, such as abscesses, tumors, Gaucher's disease, splenomegaly associated with lues, tuberculosis, malaria, Hodgkin's disease, pernicious anemia, etc. Certainly splenectomy should be considered in any case of chronic disease in which splenomegaly is present and the patient has reached the dead level of chronic invalidism, and also even in cases of disease of the reticulo-endothelial system in which there may be no clinical evidence of enlargement of the spleen. However, under no circumstances save in a case of rupture by trauma or otherwise should the

spleen be removed without a careful weighing of all the evidence secured from the history, from clinical examination and from laboratory tests.

#### CONCLUSIONS

The writer has presented this rather condensed paper concerning certain diseases of the spleen to show, first, that the spleen is not a useless organ; second, that it appears to have multiple important functions; third, that when enlarged it may be pathological; fourth, that in Banti's disease, thrombocytopenic purpura and hereditary hemolytic icterus we must make careful historical and clinical studies and tests before a differential diagnosis can be made; fifth, that splenectomy does not appear to lower the patient's resistance to infection; and finally, that acute infection undoubtedly plays a most important role in the diseases of the reticulo-endothelial system of Aschoff.

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# Abuse of Iodin, Especially of Iodized Salt, in The Prevention of Goiter\*

By C. L. HARTSOCK, M.D., *Cleveland Clinic, Cleveland, Ohio*

IT may seem presumptuous for me to attempt to discuss any phase of the relation of iodine to goiter at this time, when such an authority as Dr. Marine is to talk to you on the same subject, but my reason for doing so is that 15 percent of the total number of patients admitted to the Cleveland Clinic are goiter patients, and it is from the observation and study of this large group of cases that we have reached certain conclusions regarding the use of iodine in the various phases of this disease.

As the result of the extensive investigations by Marine and Kimball concerning the relation of iodine to simple goiter, and of those by Plummer and Boothby concerning its relation to hyperthyroidism, iodine has rightfully assumed a place of great importance in our therapeutic armamentarium. In the minds of many, however, its indiscriminate use is causing great apprehension, for the administration of iodine has been taken out of the hands of the physicians, who as a rule employ the necessary and recognized principles in selecting the cases suitable for its administration, and the public seems to have adopted for

itself the dangerous principle that if everyone would take iodine goiter would automatically cease to exist. Two factors have been largely responsible for the general adoption of this idea by the public: first, the very great commercial possibilities which the manufacture of iodized products offers and the consequent wide-spread advertising of them; and second, the extreme gullibility of the public when it is a question of believing what it wants to believe. Particularly in this locality, where the goiter problem is so vital, the public is all too prone to accept such a simple solution.

It has long been a well known clinical fact that some people are more susceptible to iodine than are others, and that one of the dangers of the continued administration of iodine is the production of symptoms of hyperthyroidism. I doubt if any clinician who prescribes this drug routinely for goiter has not had a number of cases—and perhaps not a small number—in which the thyroid has become overactive. Dr. Crile, whose clinical experience with hyperthyroidism has been so extensive, has long felt that great care and judgment should be used when iodine is prescribed in cases of simple goiter, and that careful and frequent observation of the patient is the most important point of all.

\*Clinical discussion given before the American College of Physicians at the Cleveland Clinic, February 22-25, 1927.

These conclusions were reached only after Dr. Crile had seen many cases of supposedly induced hyperthyroidism—I say supposedly, because clinical and experimental proof that iodine will induce hyperthyroidism cannot of course be presented, since this disease occurs so often in cases in which the etiological factors cannot be determined, and since attempts to produce it experimentally in animals have been unsuccessful. Our conclusions therefore must be based largely upon impressions gained from observation of the disease in large numbers of patients.

The most popular of the iodized products which have recently been offered to the public is table-salt with an iodine content of .02 percent. This is generally referred to as 'natural salt' on the supposition that this amount of iodine has been removed from the salt by the process of refining. Our attention was first attracted to this product in the summer of 1925, when quite a few unusual cases of hyperthyroidism in men were seen in the Clinic. The first one that especially attracted my attention was that of a postman who had had a large colloid adenomatous goiter for 20 years, but had always been well and had suffered no symptoms of hyperthyroidism until two weeks after he began the use of iodized salt. He was quite certain of the exact date upon which he began using the salt because his wife purchased it for the express purpose of curing his goiter. Two weeks later he began to lose weight rapidly and to feel extremely weak, and four weeks after beginning the use of the iodized salt he came to the

Clinic complaining of 'paralysis' of the legs and of a loss of 14 pounds in weight. The supposed paralysis was nothing more than extreme weakness due to severe hyperthyroidism of which he showed all the characteristic signs except exophthalmos. His goiter had rapidly decreased in size during these four weeks and according to the patient the iodized salt was 'working wonders'.

In the following six months we saw a series of 50 cases of hyperthyroidism in men, all of whom had been using iodized salt. These cases were all marked by extreme weakness, particularly of the legs, and by loss of weight. In a large percentage of these cases no goiter was present nor had there been any goiter previously—there was also no exophthalmos in the majority of the cases. Perhaps I can best emphasize the unusual type of the disease in these cases by stating that many of these men had consulted one or more physicians before coming to the Clinic and that the nature of the disease had been unrecognized, whereas in this locality the ordinary type of hyperthyroidism is usually recognized very quickly. At the present time we have in the hospital a patient who works for a salt company in Michigan, who had consulted four physicians before coming to the Clinic. He was advised by the last two to have his appendix removed and he came here in the expectation that the diagnosis of chronic appendicitis would be confirmed and an appendectomy performed. His chief complaints were weakness, a loss in weight of 70 pounds, and stomach trouble. There was no exophthalmos but his metab-



olic rate was plus 79. The symptoms in cases of this type seem to me to be such as would be produced by giving a normal person large doses of thyroid extract.

All the patients in this series who were operated upon have made splendid recoveries, but those who were not operated upon have not responded well to treatment by rest or to other therapeutic measures.

When the glands which were removed in these cases were examined histologically they showed the typical effects of the administration of iodine, for they were all in the colloid resting-state and did not have the markedly hyperplastic appearance which was so frequently seen before we began the preoperative use of Lugol's solution. As Lugol's solution had been used in only about half of these cases, and the histological appearance of all the glands was the same, the logical conclusion is that the glands had been affected by the iodine in the salt.

Another group of cases in which we feel that hyperthyroidism is induced by the use of iodized salt has included elderly women with large adenomata in whom a cardiac breakdown and auricular fibrillation has followed the use of this product. We have seen so many cases of this type that there can be little doubt about the relationship of the iodine to the initiation of the symptoms. That hyperthyroidism is the cause of the cardiac condition in these cases is proved by the basal metabolism estimation and by the improvement that follows operation.

A third group in which extreme sen-

sitivity to iodine is shown includes cases in which hyperthyroidism recurs after operation. Although it is true that cases of recurrent hyperthyroidism have always been seen, formerly they were quite rare. Since the use of iodized salt has become so common, however, they have been seen in increasing numbers; in fact, we saw ten within a period of eight months. In all these cases the return of the symptoms coincided so exactly with the beginning of the use of the salt that there could be no question but that it was the causative factor.

We have seen many other cases of hyperthyroidism besides those of the three types which I have described, in which the patients had been using iodized salt and in which we felt that the symptoms had been caused by its use. In fact, we have found by questioning that of the 2997 patients with hyperthyroidism whom we have seen within the past year and a half, 1174, or 39.17 percent, had been using iodized salt. But since, as I have already said, the etiology of hyperthyroidism is unknown, we do not feel that we have conclusive evidence of the relation of the salt to the disease in all cases.

The use of iodized salt was made general on the supposition that its iodine content was too small to have any detrimental effect. This argument and the excellent results obtained by its use in Switzerland were the chief arguments cited in its support. However, Bircher, (1) a Swiss physician, in a recent article contradicts both assertions. He states that hyperthyroidism has increased 300 percent in Switzerland since the use of iodized

salt has become general and he has observed also that small amounts of iodine administered regularly are more likely to cause iodine poisoning than much larger quantities given periodically. The fact that the incidence of hyperthyroidism has always been very low in Switzerland as compared with the region of the Great Lakes in this country, and the obvious conclusion that the Swiss are much less susceptible to this disease than we, gives this statement even greater weight.

It is interesting to note that since the wave of criticism of this salt has started, the iodine content of salt has been reduced in the state of Ohio from .02 percent to .001 percent on the advice of the State Health Department, although the labeling of the packages still remains the same. I mention this because it seems to me that in spite of statements to the contrary the advocates of this salt have recognized its dangers and have attempted to correct them without seeming to

alter their stand in the matter. It would seem to me preferable to correct the evil by having the iodine administered in a more scientific manner and with certain precautions, the chief one being the warning of adults against its use. It is possible that if children are reared on iodine, they will be able to continue its use all their lives without any danger and that in this way goiter will be completely eradicated in a few generations. Certainly no one would wish to discourage a movement which would have such far-reaching, beneficial results. In the meantime, however, it does not seem quite fair that men and women who have reached adult life with, perhaps, an 'iodine starved thyroid gland,' should now be subjected to the danger of having hyperthyroidism induced. It is entirely too easy to contract this disease anyway in this high-strung age!

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# Enlargement and Displacement of the Mediastinum\*

By R. H. McDONALD, M.D., *Cleveland Clinic, Cleveland, Ohio*

THE mediastinum is that portion of the thoracic cavity which is bounded above by the superior thoracic inlet, below by the diaphragm, posteriorly by the anterior surface of the bodies of the thoracic vertebrae, anteriorly by the posterior surface of the sternum and laterally by the mediastinal reflections of the pleura. It is divided, arbitrarily, into anterior, middle, posterior and superior divisions. The superior division lies above the level of the pericardium and of the other three, the middle division contains the pericardium and heart, while the anterior and posterior divisions are respectively the portions anterior and posterior to the heart and pericardium.

The superior mediastinum contains the arch of the aorta and the vessels arising from it, the innominate veins, the superior vena cava and the thymus gland. It is traversed by the trachea, the esophagus, the thoracic duct, the phrenic and vagus nerves and the sympathetic nerve trunks.

The anterior mediastinum is a very shallow space anteroposteriorly, and very narrow, especially above the point where the two mediastinal pleural reflections meet from the level of the

second to that of the fourth costal cartilage. This space contains a small number of lymphatic glands.

The middle mediastinum contains the heart with its attached vessels and part of the root of each lung, the remainder being in the superior mediastinum.

The posterior mediastinum contains the continuation of the esophagus and aorta, the thoracic duct, the azygos veins, the vagus nerves, and the sympathetic trunks. These structures are imbedded in a small amount of loose cellular tissue throughout which are distributed four groups of lymph glands, an anterior mediastinal group, a superior mediastinal group in front of the arch of the aorta and the left innominate vein, a posterior mediastinal group along the aorta and esophagus, and a bronchial group about the bifurcation of the trachea.

The mediastinum thus consists of a more or less elastic set of structures, which are to some extent suspended from above by the trachea, the esophagus, the great vessels and the nerves, but chiefly by the pretracheal layer of the deep cervical fascia, which runs downward on the trachea and common carotid arteries to become continuous with the fibrous layer of the pericardium. Below, the chief attachment of the mediastinum is by the fibrous coat

\*Clinical discussion given before the American College of Physicians at the Cleveland Clinic, February 22-25, 1927.

of the pericardium to the central tendon of the diaphragm. The lateral supports are formed by the reflections of the mediastinal to the parietal pleura, anterior and posterior.

The position of these elastic structures is largely determined by two systems of forces. On each side there are intrapulmonic and intrapleural pressures which act as two opposing forces, the former corresponding to atmospheric pressure except for the slight variations which result from respiratory activity, the latter being the result of the elastic recoil of the lung. Normally the intrapulmonic exceeds the intrapleural pressure by from 5 to 10 mm. Hg., and consequently the lung remains dilated; but if this relationship is altered, then the delicate balance of pressure upon the mediastinum is disturbed and in consequence the mediastinum may become displaced.

The elasticity and distensibility of the mediastinum are utilized when the anteroposterior diameter of the thorax is increased in inspiration, but all parts of the mediastinum are equally movable and it never acts as a rigid unit. The most movable structure within the mediastinum is the heart, which is capable of considerable lateral movement within the elastic pericardium.

Clinical methods of investigation will frequently reveal a displacement of the mediastinum; but on account of the anatomical inaccessibility of the area, clinical findings have frequently to be supplemented by laboratory procedures. Symptoms of compression of various structures are useful in the diagnosis of mediastinal tumors, but

in a simple displacement there does not occur sufficient alteration of position to interfere with function. Inspection may show that the trachea is deviated to one side, as judged by its relation to the suprasternal notch, and this finding may be confirmed by palpation. Similarly palpation of the apex beat may give some information, although in left-sided displacements one must be certain one is not dealing with a cardiac enlargement.

In percussion of the mediastinum one meets, on the right side, the superior vena cava and the right auricle. On the left side one perceives, from above downward, the first part of the arch of the aorta, the ascending aorta, the left auricular appendage, and the left ventricle. In this connection it is well to remember that the width of the mediastinum in the second interspace, as determined by percussion, depends to a large extent upon the obliquity of the plane of the arch of the aorta in relation to the anteroposterior plane of the body. Dr. Nichols, of this Clinic, has pointed out the many normal variations in the position of the aorta.

Percussion of the heart forms the most reliable guide to the position of the lower mediastinum. Once again one must be sure that enlargement of the heart is not present. Auscultation may reveal the change in position of the maximum intensity of the cardiac sounds. In dextrocardia this maximum intensity will lie to the right of the sternum. Frequently a systolic murmur will be heard over a displaced heart, the displacement of which is due apparently to some alteration in the outline of the mediastinum.

X-ray examination gives a great deal of information about the position of the mediastinum. In anteroposterior chest plates taken with the same degree of penetration as for the lungs, the trachea should appear in the midline as a streak of greater radiability above the cardiac density. The position of the trachea is a good guide to the position of the superior mediastinum. The position of the heart and its size can readily be seen. In many cases it will be noted that a displacement of the mediastinum is confined to either the upper or lower portions of the mediastinum.

Displacement of the mediastinum implies the presence of a structure which has not lost its normal elasticity. Normally, some loss of elasticity is an accompaniment of increasing age. Pathologically, loss of mobility is caused by the scarring which is an end-result of a local inflammatory process. Chronic mediastinitis will thus result in greater or less immobility but pleuromediastinitis or pleuropericarditis externa is frequently associated with chronic mediastinitis and the resultant contraction of the scar-tissue may cause small lateral displacements.

Unilateral tuberculosis may cause a very considerable displacement of the mediastinum or of some part of it, most notably when the lesion is on the right side. This is the result of pleural adhesions and intrapulmonic cicatrization.

There may be a well marked dextrocardia, in which, however, the apex remains to the left of the base although there is frequently some rotation of the heart in such a way that

the apex is pulled away from the chest wall and the base pressed against it. In such cases the visible apex beat disappears from the left side and is replaced by a pulsation at the right of the sternum arising at the base.

A tuberculous process in the upper lobe of either lung may result in a displacement of the upper mediastinum which is evidenced by a lateral position of the trachea. Diagnosis in such a case will be based upon the long history of tuberculosis; the small, contracted, more or less immobile side of the chest, with narrowing of the intercostal spaces; and the intrapulmonic signs.

Other pathological phenomena which cause a displacement of the mediastinum toward the side of the lesion are bronchostenosis, atelectasis and collapse. In bronchostenosis the pulmonary air is absorbed and as a result the lung volume becomes greatly reduced, so that the lung occupies considerably less space within the thorax and the space becomes filled by the increased volume of the other thoracic contents, especially of the other lung.

Displacements of the mediastinum away from the side of the lesion are seen in cases of pneumothorax and of fluid in the pleural cavity. The greatest displacements are seen in cases of spontaneous pneumothorax in young subjects in whom there has been but little inflammatory formation of adhesions. The introduction of air at intrapulmonic pressure into one pleural cavity causes an immediate retraction of the affected lung, provided there are no limiting adhesions; and as the result of the negative pressure in the other side of the thorax, the

mediastinum shifts in an effort to equalize the pressure. Moreover there is frequently a valve action about the site of rupture, so that by the respiratory movements air is actually pumped into the pleural space and high positive pressure results. The history of such a case is one of sudden acute shock with dyspnea. Examination will show the affected side to be full, possibly with widened bulging interspaces, with decreased motion under respiratory activity, tympanitic on percussion at the opposite sternal border, and the typical coin-sound will be heard. Auscultation will show the heart sounds to be absent.

In the case of a simple hydrothorax the fluid in the chest may give rise to marked displacements. In cases of empyema the formation of limiting adhesions is likely to prevent displacement. Hydrothorax is more common on the right side of the thorax in cardiac cases, on account of the pressure of the dilated right auricle on the azygos vein. Displacement of the mediastinum is thus less evident than in cardiac displacements to the right. Examination of the chest will show moderate lack of movement, fullness and dullness on percussion, relative when small amounts of fluid are present and absolute in the presence of large amounts. The outline of this dullness presents the characteristic inverted 'S'-shape, characteristic of fluid in the chest, associated with which is a triangle of dullness posteriorly adjacent to the spine on the opposite side to the fluid, this latter area evidencing the displacement of the posterior mediastinum. Breath sounds over the fluid are diminished, absent, or bronchial in

character, depending upon the amount of fluid present.

The mediastinum may be displaced in its upper or lower portion respectively by masses which protrude through the superior thoracic inlet, notably intrathoracic goiter; or by protrusions from below—chiefly diaphragmatic hernia—through the two weak spots of the diaphragm, in the area just posterior to the sternum and around the great vessels.

The suspicion of a diaphragmatic hernia will be aroused by the presence of gurgling sounds in the chest, either the stomach or large bowel being the organ usually involved. Intrathoracic goiter often produces signs of interference with the venous return to the head and upper extremities and the connection of the intrathoracic tumor with the thyroid may be palpable.

In rare instances the mediastinum may be reversed from its normal position. In these cases the heart and thoracic viscera occupy a position and relation which may be described as a mirror image of the normal. Cases in which there is a reversal of only the thoracic cavities are extremely rare, but cases in which there is an associated reversal of the structures throughout the body are much more common. Such a condition was discovered here at the Clinic in the course of the routine examination of a well developed Italian 36 years of age. His history was typical of duodenal ulcer, but otherwise he presented no symptoms. The heart was located in the right chest, the apex beat being palpable and visible in the 6th right interspace, 9 cm. from the midline,

over which the maximum intensity was heard. Examination revealed the major portion of the liver to be located on the left side, and the spleen on the right side. A reversed position of the stomach and colon was revealed by x-ray examination.

Electrocardiographic examination of cases in which there is a rotation of the cardiac axis shows an inversion of all normal waves in lead I. Lead II corresponds to a normal lead III; and lead III corresponds to a normal II.

# The Indications for and the Results of the Use of Novasurol, With Reports of Seven Cases\*

By H. M. ANDISON, *Cleveland Clinic, Cleveland, Ohio*

THE value of novasurol as a diuretic of hitherto unprecedented efficiency has come to be recognized during the past seven years. The first account of its use as a diuretic was given by Saxl and Heilig in 1920 and since that time the fact that this drug can overcome edema which has resisted the usual forms of medication has been confirmed by many observers. When used alone it is capable of increasing the output of urine in a most striking manner; but we have found, as have others, that its effect is strikingly enhanced by giving ammonium chlorid at the same time in doses up to 10 gm. per day, and also by restricting the intake of fluids and by the use of a salt-free diet.

Novasurol is the double sodium salt of oxymercurichlor-phenoxy acetic acid and veronal. It is prepared in a 10 percent neutral sterile solution. This solution contains 33.9 percent of mercury and one cc. contains one gm. of the drug. The drug is administered either intramuscularly or intravenously, but never subcutaneously, because of the resultant irritation of the tissues and the production of sterile abscesses, which heal slowly.

Novasurol was first introduced for the treatment of syphilis but for several years it has been used principally as a diuretic. It is indicated in cases of edema due to heart failure; in certain cases of edema of renal origin; in cases of cirrhosis of the liver with ascites; and in cases of carcinoma which involve the liver with resultant ascites. It is of the greatest value in the treatment of edema of cardiac origin and in this Clinic we have used it principally in the treatment of this condition and have secured remarkable results. We have also found it of value in the treatment of two cases of cirrhosis of the liver with ascites. We have not had occasion to use it in the treatment of nephritis.

I am not going to attempt to describe the action of novasurol or the physical and chemical changes which it produces in the blood, in the urine and in the fluid of the edema. It is apparent that it acts both on the kidney and on the extra-renal tissues, but it is the consensus of opinion that the kidneys play the greater rôle in the production of the increased output of urine.

During the past year we have used novasurol in the following groups of cases:—

1. Cases of cardiac failure secondary to hyperthyroidism.... 9

\*Clinical discussion given before the American College of Physicians at the Cleveland Clinic, February 22-25, 1927.



2. Cases of cardiac failure secondary to chronic valvular disease... 4
3. Cases of cirrhosis of the liver with ascites ..... 2

In all the cases of cardiac edema, without exception, the condition was desperate; there was marked edema of the lower extremities, ascites, moisture in the lungs, and in one case there was a hydrothorax on the right side. In all the cases in which the cardiac failure was secondary to hyperthyroidism, auricular fibrillation was present. In these, the subjective symptoms were marked; the appearance of each patient was characteristic—cyanosis, anxiety, dyspnea and cough. The restlessness and general discomfort were extreme. In fact, each case was of a type the treatment of which by former methods, that is, by the administration of digitalis, of xanthin diuretics and purgation, would have covered weeks and even months. With novasurol, however, the results were striking and were quickly achieved. In some of our cases only one injection was necessary; in others from two to four or five injections of one cc., at intervals of two or three days were required.

The routine management of these cases may be briefly summarized as follows:—

- (1) The intake of fluids is restricted to from 800 to 1200 cc. per day.
- (2) The diet is free from salt, and contains 40 grams of protein, and about 800 grams of fruit and vegetables, with a total caloric value of 1500 calories.
- (3) Digitalization is begun immediately.

(4) Sedatives are given as indicated by the patient's condition.

(5) Ammonium chlorid, gr. 20 to gr. 30 is given by mouth, 4 or 5 times a day.

When ammonium chlorid has been taken for two days and the urine is highly acid, novasurol is given. To test the patient's susceptibility to the drug, a small dose—0.5 cc.—is given at first; if no reaction occurs, one cc. is then injected intravenously. The digitalis and the ammonium chlorid themselves act as diuretics, but do not greatly increase the output of urine. When the novasurol is given, however, there occurs a huge output of urine. This usually begins within three hours of the time of administration of the drug and reaches a maximum in from nine to 12 hours, this maximum effect continuing for 24 hours. Frequently it continues even for 48 hours, but usually the maximum effect is over at the end of 24 hours. The total amount of urine excreted is anywhere from one to four liters and even more. The change in the appearance of the patient is very striking, as the edema becomes greatly, if not almost completely, reduced and coincident with the disappearance of the edema there is a corresponding loss of weight. It is remarkable how rapidly the ascites disappears; how the tense, swollen legs become soft; how the cough is relieved; and how much more comfortable the patient becomes and how grateful he is. The drug is repeated, if necessary, at intervals of two or three days until the edema has completely disappeared. As the heart becomes relieved from its burden, the pulse rate slows and the edema does

not tend to recur. When the edema subsides a more palatable diet is allowed and the fluid intake is gradually increased.

When the ascites is associated with cirrhosis of the liver it is important that the fluid intake should be kept low, and that a diet with a low salt content should be used. Ammonium chlorid is given as in the cardiac cases and novasurol is given at intervals of three or four days or a week. Large doses can be used in these cases. In this way the ascites can be kept in check and paracentesis is not required, or at least, is not as frequently required.

Of particular interest to us has been the value of novasurol in the preparation of thyrocardiac cases for operation. The reduction in the length of time required to prepare the decompensated thyrocardiac patient for operation is something that we have never been able to accomplish before; moreover I believe that this type of preparation not only takes less time, but is more efficient and sure than the methods formerly used. In some of these cases life has been saved for the reason that the heart could be controlled and operation be performed so much earlier. In this group of cases:—One did not come to operation as erysipelas developed and the patient died. In another, post-operative pneumonia developed and caused death. The other seven patients are doing well.

Of the group of cases in which decompensation was due to chronic valvular disease, one patient died of a coronary thrombosis some months afterward, but the edema had not returned. We have not heard from the others.

In our experience we have seen no serious toxic effects following the use of this drug. But symptoms do occur and it is for that reason that we try out the patient's susceptibility with a small dose,—0.5 cc.—before the therapeutic doses are given. Diarrhea is the most common complication we have seen, but it is of no serious consequence and is easily controlled by bismuth and paregoric and a cleansing enema. When giving novasurol it is wise not to give a purgative at the same time, as this increases the tendency to the occurrence of diarrhoea. One of our patients did have a chill and vomiting with no rise in temperature, but this quickly subsided and when the drug was again administered these symptoms did not recur. The ammonium chlorid itself may produce acidosis though this did not occur in any of our cases, as much as 170 grams of ammonium chlorid having been given without any harmful effects. I think that acidosis is more likely to occur in cases of nephritis with a retention of nitrogen, and in these cases the use of novasurol is attended with considerable danger. Should acidosis develop, however, it is readily combatted by the administration of alkalis.

#### CASE REPORTS

*Case I (143844).* A woman 27 years of age. The diagnosis was recurrent hyperthyroidism. The patient's heart was markedly enlarged, was fibrillating, and was badly decompensated. Edema was present in the lower extremities and in the abdominal wall. The abdomen was distended with fluid. Breathing was difficult and the patient was very restless. *Treatment:*—restriction of diet and of fluids (1000 cc.); tr. digitalis, 2 cc. every 4 hours; ammonium chlorid by mouth, 20 gr. every 4 hours. The

fluid output was very low. On the third day 1 cc. of novasurol was given, the fluid output on that day was 3790 cc., and by the sixth day the patient had lost 19 pounds in weight. Novasurol was again administered on the eighth day and again there was a very large output of urine. By the tenth day there had been a further loss of 10 pounds and the edema had entirely disappeared. As it had not reappeared by the twenty-first day, a lobectomy was performed. Following the operation the patient had a very severe reaction, pneumonia developed, and death occurred on the fourth day after operation.

*Case II (169457).* A woman 55 years of age. The diagnosis was very severe hyperthyroidism with secondary myocarditis and acute heart failure. Auricular fibrillation was present, also generalized edema and ascites, and both lungs were full of moist râles. *Treatment:*—restriction of diet and of fluids; tr. digitalis. The pulse became slightly lower and the output of urine was fairly good by the fifth day. The administration of ammonium chlorid was started and on the eighth day 1 cc. of novasurol was given. The urine output for this day was 2160 cc. Novasurol was again administered on the twelfth day, with a resultant output of 2250 cc., and of 2075 cc. on the following day. By this time the patient had lost 28 pounds in weight and was very comfortable. The pulse was about 80, but was still very irregular. Ten days later a lobectomy was performed, the patient stood the operation very well and was discharged on the tenth day after operation. She was last seen four months after the operation, and while her heart was still fibrillating, it was compensated.

*Case III (175579).* A woman 52 years of age. The diagnosis was very severe hyperthyroidism with secondary myocarditis and acute heart failure. Auricular fibrillation was present, also generalized edema and ascites, and both lungs were full of moist râles. The pulse was 140 and very irregular. On the second day the temperature rose to 104° and there were definite evi-

dences of bronchopneumonia. Treatment for the massive edema seemed to be most urgently indicated, and the following measures were employed: Restriction of diet and of fluids; tr. digitalis; morphia for restlessness; ammonium chlorid by mouth. On the third day 1 cc. of novasurol was given. The output of urine on that day was 2100 cc. Novasurol was again administered on the fifth day, with a resultant fluid output of 4130 cc., and the edema disappeared except for a small amount in the lower extremities. After the third dose of novasurol on the seventh day, which again caused a large output of urine, the edema entirely disappeared. By the tenth day the temperature was normal and the signs of pneumonia had almost entirely disappeared. The pulse was 90, but was very irregular. A week later the edema reappeared. Two doses of novasurol were given, at an interval of two days, and the edema again disappeared. The total loss in weight was 36 pounds. On the twenty-sixth and twenty-eighth days x-ray therapy was applied to the thyroid gland, in order to diminish its activity. The patient was discharged five days following the last treatment, with a normal temperature, pulse 80 but irregular, no edema. She was able to be out of bed and to walk around. She was last heard from one month later and at that time was in fairly good condition, the heart being compensated.

*Case IV (161366).* A woman 49 years of age. The diagnosis was acute heart failure secondary to hyperthyroidism. The patient was practically *in extremis*, the abdomen being markedly distended by fluid. *Treatment:*—restriction of diet and of fluids (800 cc.); tr. digitalis, 2 cc. every 4 hours; ammonium chlorid, 20 grs. every 4 hours. On the second day 1 cc. of novasurol was given with a resultant fluid output of more than 2000 cc. On the eighth day novasurol was again administered, the fluid output on this day being 2100 cc. and on the following day 1900 cc. As the edema had entirely disappeared and the heart-rate was 90, the ammonium chlorid was discontinued and the fluid intake and the diet were increased. For the next three days the patient was

very comfortable, then her temperature rose sharply to 102.6, and on the following day she had a typical erysipelas of the face. The temperature continued to rise, the erysipelas spread, and death occurred one week after its onset. The edema had not returned and I feel that this patient would have made a good recovery and that operation could safely have been performed had the complication not developed.

*Case V (163101).* A woman 41 years of age. The diagnosis was hyperthyroidism with secondary myocarditis and cardiac failure. *Treatment:*—Karell diet, tr. digitalis and xanthin as diuretics. No diuresis was produced and the patient's condition did not improve. On the seventh day ammonium chlorid, 20 grs. four times a day, was given, two days later 1 cc. of novasurol was administered intramuscularly, and this was repeated daily for three days, without, however, producing any diuresis. On the fourteenth day 2 cc. of novasurol was given intravenously, with a resultant fluid output of 2800 cc. on that day and of 2075 cc. on the following day. On the next day the novasurol was repeated with a resultant output of 3900 cc. and of 3625 cc. on the following day. The edema had completely disappeared, the patient's condition was improving gradually, and on the thirty-third day after she entered the hospital lobectomy was performed. The patient stood the operation well and left the hospital nine days later. When she returned three months later for the second lobectomy, the heart was again decompensated but not to the same degree as on the previous admission. Ammonium chlorid and novasurol were again employed, with good results, and the second lobectomy was performed 26 days after the patient entered the hospital. She was discharged nine days later and since then has been in fairly good condition. By taking extra precautions her heart has remained compensated.

*Case VI (175859).* A colored man 58 years of age. The patient complained of having been short of breath for the past

six months. The diagnosis was myocarditis, probably luetic in origin, as the Wassermann test gave a finding of 4 plus. The liver was tremendously enlarged, the abdomen was distended with fluid, and edema was present in the whole trunk and in all the extremities, the legs being so swollen that the skin had broken in places. *Treatment:*—special diet; restriction of fluids (800 cc.); ammonium chlorid, 80 gr. per day; novasurol, 1-2 cc. about twice a week. At the end of 25 days the patient had lost 48 pounds in weight and there was only a small amount of edema, this being around the ankles. At this time the patient left the hospital against advice, claiming that he felt so well he did not consider further treatment necessary, and he has not been seen since.

*Case VII (176692).* A woman 44 years of age. The diagnosis was cirrhosis of the liver. The abdomen had been enlarged for only two months. One week before she entered the hospital the distension had become so great that her physician had performed a paracentesis and had withdrawn about two quarts of fluid. The fluid had collected again very rapidly, and as the patient was very uncomfortable upon admission, paracentesis was again done and 7700 cc. of fluid were withdrawn. *Treatment:*—special diet and restriction of fluids (800 cc.); ammonium chlorid, 80 grs. per day; and novasurol, 1-2 cc., given intravenously every four or five days. The ascites was kept in check by this treatment for a month. At that time it was decided, since the novasurol treatment was such a slow process, to give the patient the small chance offered by the Talma-Morrison operation. This was performed and a drainage tube was left in the wound for 8 days. Twenty-one days after operation the abdomen was so distended with fluid that a drainage tube was again inserted. Seven days later the patient died suddenly. I feel that the patient would have lived quite comfortably and for some time if the more conservative measures had been continued, for the ascites was being controlled very efficiently by the use of novasurol.

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# Ocular Disturbances in Diabetes\*

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**D**EFINITE changes are found in the eyes of a large number of patients in whom there is an increased blood-sugar content. One of these changes is functional, the rest are pathological. It is important for the physician to be able to recognize these various changes, not only that he may institute appropriate local treatment but also because of their diagnostic significance.

The only functional disturbance associated with hyperglycohemia is that called *glycosuric amblyopia*, in which the patient has a definite loss of vision without any evident cause. The visual fields show a central loss of color—of red, of green, or of both; they sometimes show a peripheral contraction; and rarely hemianopia (de Schweinitz). Several observers have reported that this type of disturbance is found most frequently in tobacco-users.

As loss of vision, however, may be the only symptom of an increased blood sugar content, it is important to examine the blood in any case of loss of vision of unknown origin. The treatment is confined to treatment of the general condition and to restriction of the use of tobacco, if that is indicated. In these cases the condition is

likely to clear up and vision to be restored in great part.

It is not unusual for diabetic patients to have trouble with glasses which have recently been prescribed, or to demand frequent changes. The eye-changes which cause this trouble are usually in the refractive media. Excluding those refractive changes which are due to early cataracts, these changes are of two main types: first, increased far-sightedness, or hyperopia; second, near-sightedness, or myopia.

Cases of the first type have been reported in which the *hyperopia* has attained three diopters. It is thought that this condition is caused by a decrease in the fluid content of the eye, which results in a shortening or a change in the lens itself. Patients suffering from this disturbance usually are relieved by treatment of the diabetic condition, and unless the need is imperative, their glasses should not be changed or new ones supplied until the blood-sugar curve has been fairly stable for a month or longer.

Inability to use the eyes within a range of less than from 18 to 25 inches is often due to *early presbyopia* due to the diabetic condition, for as a rule physiological presbyopia does not appear before the age of 40. This early presbyopia is usually more or less transitory, and if glasses are pre-

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scribed at once they will be too strong after the diabetes has been controlled.

In cases of the second type the myopia is frequently due to a change in the lens similar to that found in the early stages of senile cataract, which results in the so-called 'second sight'. In these cases the lens is probably swollen and unless cataractous changes set in, the difficulty will right itself when the diabetic condition is controlled. The patients in this group frequently have headaches which are not relieved by glasses, because of the instability of the refractive media. For this reason, in any case in which persistent or recurrent headaches are unrelieved by glasses a blood sugar determination should be made.

Weakness or *paralysis* of individual eye-muscles or of groups of them is often a clue to the diagnosis of diabetes. Patients who complain of a sudden ocular disturbance which causes them to see double or to have vertigo should have the various eye-muscles investigated, as they may be completely paralyzed. The muscles supplied by the third nerve are most frequently involved, because the third nerve supplies all but two muscles—the lateral rotator or the external rectus, which is supplied by the sixth nerve; and the superior oblique, which is supplied by the fourth. Whether or not the fourth nerve is affected can be determined by questioning the patient or by employing the various muscle-balance tests. Palsy of the fourth nerve occurs so rarely, however, that it is necessary only to determine whether the third or the sixth is the affected nerve.

Cases of diabetes have been record-

ed in which there has been a disturbance of accommodation-convergence, that is, an inability to keep an object fused when within reading distance, although it can be seen clearly at this distance with either eye alone.

Ocular muscle palsy is due to diabetes frequently enough to warrant a blood-sugar determination in all cases in which the etiology of the ocular disturbance is unknown. It is not known whether the muscles or the nerve itself is involved in these cases. In the majority of cases the palsy tends to clear up or to improve greatly under general treatment for the diabetes. As for local treatment, the vertigo or diplopia may be relieved by merely pasting a patch over the glass for the offending eye. In cases of long standing the patient learns to suppress one of the images. If the paralysis has been of long duration, surgical intervention may be necessary to give relief.

Diabetic patients sometimes suffer from smarting and burning of the lids, with increased lacrimation and pain on exposure to light (photophobia.) In these cases a lowgrade *conjunctivitis* is sometimes found to be present. Whether this is secondary to a diabetic retinitis or whether it is a separate feature of the diabetes has never been determined. Soothing eye-washes and dark colored lenses frequently give relief.

Discoloration of the skin and of the conjunctiva in association with diabetes is known as *xanthelasma* or *xanthoma*. In a case which we have seen retinal lipemia and xanthelasma were coincident and both conditions cleared up as the diabetic condition

became controlled. Parker quotes Johnson as saying that diabetes may develop in patients who are suffering from xanthelasma.

*Iritis* is a frequent complication of diabetes. Exudates may appear, and minute hemorrhages may take place, filling the pupillary area and fixing the pupil. It is not unusual for such an iritis to be of a low grade but disastrous to vision (Parker). A thinning or an atrophy of the iris is not uncommon and this may be secondary to the iritis. The symptoms of iritis are inflammation of the eye, pain and photophobia, and sometimes loss of vision. In any case of iritis of uncertain etiology a blood-sugar determination should be made.

An injury of the iris either of accidental or surgical origin in a case of diabetes is often very harmful, as in spite of treatment it may lead to a chronic disturbance with final permanent loss of function and of vision. Fuchs describes a dropsical, bleb-like change in the iris which he claims is due to diabetes.

The cause of the iritis which is associated with diabetes is thought to be an auto-intoxication due to the lowered resistance of the parts, with secondary infection. Good results often follow treatment of the diabetic condition supplemented by local treatment, that is, by putting the eye at rest by keeping the pupil dilated with atropin and by having the patient wear dark glasses. In these cases one must always watch for indications of secondary glaucoma and the patient should be instructed to consult the oculist if any unusual symptoms arise.

Changes in the lens which may accompany diabetes have already been mentioned. These vary from granular or minute deposits to bluish-white 'skimmed milk', radiating streaks. *Cataracts* occur, even in children; in fact, there are four such cases now on record. A diabetic cataract in an adult usually develops more rapidly than the senile cataract. One case was seen at the Cleveland Clinic in which a hazy condition of the lens changed to a complete cataract in a month. In these cases the cataracts are usually bilateral. In these cases there is frequently a very high blood-sugar content, although in the case which we have mentioned the cataract continued to develop while the patient was under treatment and after the blood-sugar level had become normal.

In any case of cataract in a child or in a young adult in which there is neither a history of trauma nor an hereditary factor, diabetes should be suspected. These patients complain of an ever-present mist or veil over their eyes, which they continually attempt to wipe away. If the changes involve the pupillary area the loss of vision is greater than if the periphery of the lens is involved. The changes are posterior-polar or posterior-cortical and are not associated with iridocyclitis (Klein). They are probably due to an alteration in the content of the lens, either an increased sugar content or a lack of nutrition.

The treatment indicated is treatment of the diabetic condition, in the hope of preventing further development of the local disturbance. In some cases the change in the lens may clear up to a certain extent. Surgical treatment



is indicated if the patient is handicapped by his misfortune, but it should be undertaken only after the diabetes is under control. These patients do not always do well, and if one attempts an operation one runs the risk of 'lighting up' an old uveitis or some other focal infection. The success of the operation in these cases depends as much upon the treatment for the diabetes as upon the skill of the surgeon. However, the less trauma that is produced, the better the end-result, for the tissues of diabetics do not react favorably to injury.

*Retinitis* is frequently associated with diabetes and it usually occurs when the disease is in a late stage. The patient complains of a loss of vision, of photophobia, of floating spots, etc. Examination of the fundus reveals small, punctate, brilliantly white spots, or yellowish-white spots, which are usually discrete, and which sometimes coalesce to form larger patches. They rarely simulate albuminuric retinitis, in which the patches usually form a stellate figure in the macular region. The majority of the punctate spots are in the neighborhood of the central area. There are frequently present minute punctate extravasations of blood which are quite different from the flame-shaped changes associated with nephritis. Vitreous hemorrhages are not uncommon and subhyaloid hemorrhages have been observed.

Wagner and Weder conclude that the primary cause of the retinitis which is associated with diabetes is found in the pathological change which takes place in the vascular system. This view is also held by Cantonnet and others.

A special form of retinitis known as *lipemic retinitis* is sometimes associated with diabetes. At least 28 cases have been reported in the literature (Gray, Root). In these cases the vessels appear to be of equal size and their appearance has been variously described as 'salmon', the 'color of ground glass', 'strawberry and cream', 'waxy', 'creamy', 'milky', or of a 'milky sheen'. The retina is hazy; there is usually little change in the vision; and there are usually no hemorrhages or exudates. This form of eye-change is usually seen in young adults under the age of thirty-five.

The blood shows a high fat content and the urine often contains fat. The fundus-change may be due to an increased amount of fat in the blood, in the adventitia, or in the surrounding tissues. The general prognosis is usually grave; Gray reports a mortality of 57 percent, most of his patients dying in coma. In a case reported by Gray and Root, the patient recovered, and in one seen by the author with John the recovery was complete, with no loss of vision or other defect.

That diabetic patients have retinitis is well known; and that they have retinal changes consisting only of hyperemia, without exudates or hemorrhages and without noticeable vessel-changes, has been noted. Although in many cases vascular changes are present, I do not believe that this entire group should be classified as of vascular origin.

The treatment is directed entirely toward improving the general condition, while as complete ocular rest as possible is prescribed. The prognosis as to vision is poor if the macular re-

gion is involved; the areas involved in exudates become atrophic, and rigid dietary measures and the rest of the usual routine treatment for diabetes offer the only means of relief.

In some cases of diabetes the *optic nerve* is involved in an inflammatory process similar to that seen in acute attacks of the exanthemata or of sinus trouble. The disc shows a haziness with a blurring of the borders; there is increased tortuosity of the vascular system; and not infrequently an associated retinitis. The patient suffers from bright light, and may have a loss of vision. The prognosis is good and general diabetic treatment usually assures relief.

*Lowered intra-ocular tension* in a case of diabetic coma has been reported by Riesman and Middletown. In the cases which the author has seen in coma the tension, which was measured by the Schiötz tonometer, either showed no change or was increased. In one case, that of a young girl, the tension was 57. This unusual rise may have been due, of course, to the treatment, as the tension was taken shortly after the injection of insulin; however, that was not true in other cases in which also the tension was above normal. In all the cases in

which the tension was increased it later became normal.

Parker reports an interesting case of *glaucoma* which failed to respond to surgical treatment, although repeated examinations of the urine showed no sugar, a blood-sugar test showed a content of 250 mg. per 100 cc. The treatment which reduced the blood-sugar content also relieved the ocular condition. The relation of intra-ocular tension to glaucoma is unknown, however this case calls attention to the possibility that diabetes may be a causative factor in some cases of glaucoma.

In conclusion let me call attention once more to the importance of recognizing the ocular disturbances which may be associated with diabetes. When one observes how frequently they occur, one is convinced that all patients who have ocular symptoms or signs the origin of which is unknown should have a blood-sugar test, or better still, a glucose tolerance estimation. It is also important that all diabetic patients with ocular disturbances should have local as well as general treatment, but emphasis should be laid upon the importance of repeated estimations of the blood-sugar content, for it is only by keeping the diabetic condition under control that one can hope to relieve the ocular condition.

## Editorial

WITH this issue the Annals begins a new series under a new name "The Annals of Internal Medicine." Many of the members of the College have felt that the old title was too broad, and that "Internal Medicine" should be substituted for "Clinical Medicine" as indicating more precisely the especial field of endeavor of the College. The latter should stand for internal medicine as the American College of Surgeons stands for surgery. This function has not yet been adequately taken up by the College, as the early years of its existence have been so largely given up to organization and establishment on a firm and permanent foundation. This, we believe, has now been accomplished, and the College can now turn its energies actively into taking up for consideration the various problems affecting its especial field. Organized internal medicine has not yet accomplished for the hospital what surgery has been able to do. In consequence it suffers because of its lesser importance in the hospital economy, and as a result its hospital position has not received as complete a standardization as has surgery. The new title will indicate more definitely the function of this association as intended for internists primarily. During the organizing period of the College it has not had full control of its journal either by copyright or finan-

cially. This inevitably led to a situation necessitating change. The College must own its journal and have full control of it. The Committee in charge of this problem has fully decided upon this policy, and the College in the future will be the owners and assume the entire responsibility of its publication. In other terms, the College will be the publisher of its Annals. This means for one thing that monthly publication and increased number of pages can be carried out as planned three years ago without too great a cost to the College. The editor will have responsibility only for the material and its prompt publication. A means for more regular publication has been found in the location of editorial office and printer's establishment in the same city, and a new rule as regards proof. The editor's labors have been greatly handicapped by the failure of authors to send in manuscript or to return proof within a reasonable time. It has been almost impossible to secure from those who have presented papers and given addresses at the Clinical Congress copies of these in time for prompt publication. In spite of the rule of the College that all material delivered before it becomes its property for publication in its annals, various invited guests have wholly disregarded this and the College has failed to publish all of the

material offered before its convocations and general meetings. Although a special effort was made to secure a complete publication of everything presented at the Clinical Week in Cleveland, half a dozen or more of the addresses given could not be secured for publication. It is hoped that this situation will be wholly done away with at the New Orleans meeting, and that for the first time the College may be able to publish in complete form all of the material presented in the general meetings. In addition to this it seems also desirable that the most important clinics given during the Clinical Weeks should be put on record in readable form. The work presented to the College at these meetings should be of such a high order that it should deserve a permanent record in the annals of the College. The recording of the Clinical Week, however, is not the only function of the Annals. The editor believes that the College should publish a journal in which valuable contributions from its members not presented at the meetings should have an available opportunity for publication. The Annals should become a record, not only of its meetings but also of the achievements of its members. Articles from the Fellows and Members of the College are therefore solicited by the editor for this journal. The right to go outside of the College for suitable material bearing upon internal medicine will also be exercised by the editor, and he will seek to obtain from leaders in medical re-

search, both in this and in other countries, valuable material of interest to the College. The cultural side of medicine, as well as the scientific and purely clinical, will be represented in these articles. Particularly does the editor hope that the historical side of internal medicine will receive a goodly recognition. The editorial pages will be increased, and it is hoped that the subjects chosen for these will include matters especially interesting to the readers of the journal. The abstract will be chosen for their apparent value, either as dealing with new investigations or summing up old knowledge, whether negative or positive in result. Finally, the reviews will be devoted to new publications especially in the line of internal medicine, but also of general cultural interest relating to medicine. The News Notes will give information concerning the activities of the College and its members. To sum up, the editor hopes that the coming volume for 1927-28 will contain a complete record of the New Orleans meeting, valuable articles on internal medicine by Fellows of the College and others not members of the College, so that it may become a publication regarded as unique in the field of internal medicine, and of value, not only to the members of the College, but to all physicians concerned with the practice of internal medicine. He asks the cooperation of the college in bringing this aim to a successful issue.

## Abstracts

*Four Cases of Tularaemia (Three Fatal) with Conjunctivitis.* H. L. FREESE, G. C. LAKE and EDWARD FRANCIS (Public Health Reports, February 26, 1926.)

Tularaemia was demonstrated by animal inoculation and by cultural and serological methods in the sole survivor of an outbreak of a glandular febrile affection with conjunctivitis occurring in four members of a family living in Virginia, three of whom died without tests for tularaemia having been made, either before or after death. The four cases became ill within a 24-hour period and onset was sudden, the father was nauseated, complained of headache and had chills; the three children vomited, and the boy in addition had convulsions. Within 24 hours after the onset, all had axillary temperatures of  $103^{\circ}$ - $104^{\circ}$ , conjunctivitis, and swollen lymph glands in the parotid region. There was no skin eruption, and no throat symptoms except some redness. The cervical and axillary glands became much enlarged; there was no evidence of lung involvement and no rigidity or spasticity suggestive of meningitis. All showed the picture of an extreme grade of febrile intoxication. No autopsy was held on any one of the three fatal cases. Swabs taken from the nose and throat of the surviving child and used for rabbit inoculation produced typical

tularaemia in six guinea-pigs; and transfers made from these by subcutaneous injection and scarification to 14 others produced death in all with typical lesions of tularaemia, and from these *Bacterium tularense* was isolated in pure culture. The blood serum of the survivor was found to agglutinate *Bac. tularense* in all dilutions from 1:10 to 1:1280 but not in higher dilutions. Although details as to the source and method of infection are wanting, there was abundant proof of contact with rabbits, and the proof of the cause of the illness in the surviving patient justifies the conclusion that all were cases of tularaemia. Whether certain members of the family in dressing infected rabbits transferred the infection by their hands to their conjunctiva, or whether insufficiently cooked rabbit was eaten are matters of conjecture only, but the evidence seemed to point to primary infection of the conjunctiva. It is of further importance to learn that an epidemic had occurred among the rabbits of the neighborhood during the previous May. Tests made in the cooking of infected rabbits proved conclusively that infected rabbits when insufficiently cooked are dangerous as food.

*Zur Biologie des Carcinoms. IV Mitteilung.* FRITZ SILBERSTEIN, JOHANN FREUD, TIBOR RÉVÉSZ and BLANKA SCHNEID. (Zeitschrift für

die gesamte experimentelle Medizin, April 28, 1927, page 56.)

In February, 1925, these authors reported that they had discovered that experimental mouse tumors were influenced by insulin. This has been confirmed by Münzen and Rupp, Watermann and von Witzleben; on the contrary Bauer and Nyiri could not confirm their results. The authors have therefore continued their work with the following results. Mice that are being treated with tar-painting for the production of tumors, when treated at the same time with insulin show an inhibition of tumor production. Some of the mice so treated remain tumor free or after a certain time die tumor free, while control animals showed tumors. In the insulin treated tumors the precancerous nodules developed much later than in controls; likewise the malignant transformation of these occurred much later than in controls. The life-duration of the insulin treated animals was much longer than in the controls. In the case of mice that had developed small warts as the result of the tar painting, the further development of these warts was inhibited by protracted insulin treatment, and the duration of life prolonged. When animals belonging to a 100 per cent carcinoma strain were employed for tar painting or inoculated with carcinoma, and treated with insulin, tumor production was inhibited. Some mice remained tumor free; a relatively large number of the mice died tumor free during the treatment, while control animals showed more or less large tumors. In a certain per-

cent of animals the development of the tumor was delayed; in another percentage the tumors after a primary inhibition grew to a large size but were apparently well borne by the animal, the life duration being much longer than in the case of the control animal. The insulin effect was found to be enhanced when certain amounts of dioxyacetone (Oxantin) were combined with the insulin.

*Versuche, inoperable Carcinome mit Insulin zu behandeln.* FRITZ SILBERSTEIN, JOHANN FREUD and TIBOR RÉVÉSZ. (Zeitschrift für die gesamte experimentelle Medizin, April 28, 1927, page 78.)

On the basis of their experimental work with tar and inoculation carcinoma in mice in which these authors found that a relative immunity could be produced by the administration of insulin, and that this was more striking in animals in which dioxyacetone was given in connection with the insulin, they have applied this treatment to inoperable human cases of carcinoma. Sixteen of these were treated systematically for a long time and fifteen cases for a shorter period. Inasmuch as the majority of cases of carcinoma observed by these workers showed a high degree of insulin tolerance, yet there were some cases that bore only small doses (about 120 units) per day. As a result of their treatments the authors found that the fasting blood-sugar values are above the normal in untreated carcinoma cases. During the course of insulin treatment this value varies. Almost

always periods of increased fasting blood-sugar values occur, followed by a return to normal. When the blood-sugar curves of fasting carcinoma patients and healthy persons are compared certain differences are observable. The first part of the insulin effect in cancer patients is characterized by a slow fall, while the second part is characterized by a rapid rise suggesting that in diabetic cases. The blood sugar values of carcinoma cases rise under the influence of an absolute carbohydrate-free diet, also suggesting the curve in diabetes. This relationship is also demonstrable when insulin is injected shortly before the meal time. Almost all of the cancer patients treated by the authors were in a bad general condition. They reacted, with few exceptions, after a few days, with definite improvement of general feeling and increase of strength. It appeared as if insulin treatment kept continually on the border of tolerance inhibited for some time the growth of the tumor and its spread. In one case of uterine cancer the growth remained stationary for over a year. In other cases, during the course of the treatment, a decrease in the size of the tumor and metastases and sharper demarcation were seen. Softening of the tumor masses was produced by direct local injection of the tumor. In the case of accessible tumors moderate doses (60-100 units) were sufficient,

that were in general well borne. Injections of larger doses into larger tumors produced no acute hypoglycemic symptoms, but were followed by a condition of intoxication which the authors ascribed to a toxic destruction of albumin, in that it did not respond to a parenteral administration of sugar or to carbohydrate feeding. Sudden breaking off of the insulin treatment was followed by a rapid change for the worse. Gradual cessation of treatment was followed by the same result after some months from the last treatment. The insulin treatment, as in the case of diabetes, must be continuous, or interrupted with great caution and resumed after a not too great interval. The authors believe that insulin treatment in the case of radical operation may be of use in protecting against recurrence and in improving the general symptoms. They recommend also the use of oxantin to increase the action of the insulin, and also that of ergotamin to increase the sympathetic tonus. After systematic insulin treatment a period of maximum tolerance is sooner or later reached; and in these cases in which a direct action upon the tumor was noted, this was coincident with this stage. After long continued insulin treatment the resistance again rises until a record maximum of tolerance is reached.

## Reviews

*Lectures on Internal Medicine* (Delivered in the United States, 1926). By KNUD FABER, M.D., Professor of Internal Medicine, University of Copenhagen, Denmark. 147 pages, 43 figures and charts. Paul B. Hoeber, Inc., New York, 1927. Price in cloth, \$3.00.

The four lectures here presented were given during a visit to the United States in February and March, 1926, made under the auspices of the American College of Physicians, the College of Physicians of Philadelphia, the Medical Schools of Baltimore and Boston and the Rockefeller Institute of Medical Research. These lectures were on the following subjects: "The Etiology and Pathogenesis of Achylia Gastrica," "The Intestinal Origin of Pernicious Anemia," "Benign Glycosuria" and "Historical Outline of Medical Therapy, A Sketch." The first of these constituted the Nathan Lewis Hatfield Lecture of the College of Physicians of Philadelphia, February 12, 1926; the second was delivered before the American College of Physicians, February 22, 1926; the third was the Herter Fund Lecture at Baltimore, February 18, 1926; and the fourth was the Harvey Lecture at the New York Academy of Medicine, March 13, 1926. These lectures are beautifully printed in a volume of convenient size. They are original, stimulating and most readable, written in the easy, flowing and distinguished English characteristic of Faber's writings in this language. In the first lecture he maintains his thesis that the very common and important disease called achylia gastrica has nothing particularly remarkable in its etiology and pathogenesis to mark it out from the diseases of other organs; the proper term for the disease is gastritis, by which is to be understood, not the old conception of gastric catarrh, but a disease of the glandular parenchyma of an

inflammatory nature. When it is excited through nervous channels, it can only persist for a short time, but apart from this it is due to the same causes which we know produce disease in other organs; direct irritation or hematogenous intoxication by bacterial toxins or autotoxins. The disease is analogous to nephritis and hepatitis, and gastritis should take its place side by side with these diseases. In the second lecture Faber expresses his conviction that pernicious anemia has its origin in intestinal intoxication. Achylia gastrica (anacidity) is the most frequent but not the only cause of idiopathic pernicious anemia. A continually occurring intoxication is the most natural explanation, and in the majority of cases it is an intestinal intoxication by protein toxin. This is the case with Bothriocephalus anemia, stricture anemia, sprue and anemia occurring in patients with achylia. In pregnancy, sepsis and perhaps in syphilis, we must look for the production of toxin elsewhere. The problem of family and hereditary predisposition must be considered in connection with each of these causes. The third lecture is also an interesting compilation of the known facts on benign glycosuria and the glycosuric threshold. Two essentially different forms of glycosuria exist; the first, true diabetes, is due to disease of the islands of Langerhans; the second form of glycosuria is due to deficient blood sugar regulation, and is either due to an habitually abnormally low threshold or an habitually abnormally high alimentary blood sugar rise. In some cases both conditions may be observed. In all of these cases it is, however, a matter of individual constitutional abnormality rather than disease. These abnormalities are harmless to the individual and deserve to be estimated as such by physicians and insurance companies. The practical sig-



nificance of a knowledge of the benign glycosurias cannot be overestimated. Many patients come to be regarded as true diabetics when, in fact, they had only an insignificant passing glycosuria. On account of the extensive occurrence of these non-diabetic forms of glycosuria the correct interpretation of glycosuria is of the very greatest importance to the patient. The question can be determined only by the careful study of the glucose contents of the blood, and we possess the means of doing this in the micro-methods introduced by Bang, and elaborated by Hagedorn and Jensen. The whole development of blood sugar estimation is a fine example of the advantages of exact laboratory analyses. The fourth lecture consists of a sketchy historical outline of medical therapy, and in itself is so interesting that one regrets that Faber did not elaborate this historical study into a volume by itself. It is to be hoped that he may do this later. The development of modern therapy is traced through the periods of "bleeding" pharmacological experimentation, drug-therapy, "Naturheilkunde," hydrotherapy, massage, dietetics, gland-therapy, serum therapy and modern chemotherapy, with the present-day tendency towards "etiotropic remedies," that is, remedies directed towards the specific cause of the disease in the endeavor to effect a really specific and total cure. This last lecture is all too short, and one finishes with the wish that it had been elaborated into a more complete and finished study. The volume is a good example of the class for which Hoeber is becoming noted as a publisher—medical historical studies of prime cultural value, and not mere textbooks. As we have pointed out in other reviews of books issuing from the Hoeber Press, one may find in these productions books that serve particularly well as presentation volumes for physicians and medical students. We take pleasure in recommending this volume of Faber's lectures as the latest addition to this most desirable collection of publications dealing with the cultural side of medicine.

*Hypotension.* Medicine Monographs, Volume XIII. By ALFRED FRIEDLANDER, Professor of Medicine, College of Medicine, University of Cincinnati. 193 pages. The Williams and Wilkins Company, Baltimore, Maryland, 1927. Price in cloth, gold stamped, 6x9, \$2.50.

This volume is the first critical and analytical study of the literature of low blood pressure, and presents a summary of our knowledge on this subject. It will, therefore, be of great interest to practicing physicians and surgeons, life insurance examiners, biologic and physiologic chemists and pharmacologists. The volume begins with an introduction defining low blood pressure in its relationship to health and disease. The clinical methods of estimating blood pressure are given in detail, with a summary of the results of studies of normal blood pressure in the newborn, in childhood and in adult life. Hypotension in apparently healthy whites is then taken up, with a discussion on blood pressure in states of sleep, muscular exercise, relation to body weight, and the factors entering into the maintenance of blood pressure. The various types of hypotension are described. Temporary hypotension in anaphylactic shock, traumatic and surgical shock, relationship of blood pressure to general, local and spinal anesthesia, clinical studies of blood pressure during operations and the treatment of normal and surgical shock are adequately treated; then follow sections on hypotension in acute and chronic diseases and the constitutional diatheses, the relation of hypotension to certain mechanical factors, and the action of tissue and gland extracts and drugs on blood pressure. Pressor and depressor drugs are considered in respect to their blood pressure actions. There follows then an adequate section on essential hypotension, and hypotension due to malfunction of the factors that normally maintain blood pressure: the cardiac factors, the condition of the vessel walls, peripheral resistance and vasomotor tone. Following this there are sections on hypotension in relation to endocrine disorders (adrenals, pituitary gland, gonads, pluri-

glandular disturbances and interglandular associations) with clinical studies, discussion of glandular therapy, endocrine asthenias, present achievements and future prospects of organotherapy. All of these sections contain valuable material, and its assembling in this condensed form makes this volume of great value to the student and practitioner. The volume closes with a general summary and a bibliography of three hundred and seventy-five reading references. This work must be regarded as an essential to be included in any internist's working library.

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*The Human Body in Pictures.* A Visual Text of Anatomy, Physiology and Embryology. By JACOB SARNOFF, M.D., Associate Surgeon, United Israel--Zion Hospital; Attending Surgeon, Harbor Hospital; Consulting Surgeon, Infants' Home; formerly Associate and Instructor of Anatomy, Long Island Medical College, Brooklyn, New York. With Foreword by John Osborn Polak, M.D. 120 pages, and

190 original illustrations, mostly from dissections and animated drawings by the author. Physicians and Surgeons Book Company, Brooklyn, New York. Price in cloth, \$2.50.

This is an illustrated teaching manual that follows closely and describes in detail the various anatomical and physiological facts as presented in the motion picture reels and still picture films of "The Human Body Series." These sets can either be purchased outright or rented; the motion pictures are distributed by the Edited Picture System, Inc., New York; and the still picture films by the Bray Screen Products, Inc., of New York. This series of films is intended primarily for students of anatomy and physiology and is especially adapted for use in schools, colleges, nurses' training schools, departments of physical education, etc., to give the lay mind a clear understanding of the essential structures and functions of the human body. For medical students and graduates they may be of use as visual aids in review courses.

# College News Notes

## Obituaries

Dr. John Reynolds Brown, Tacoma, Washington—May 7, 1927. Heart Disease. Elected a Fellow of The College February 23, 1920.

Dr. Frank Edwin Coulter, Santa Ana, California—July 18, 1927. Coronary Sclerosis. Elected a Fellow of The College February 8, 1921.

# Functional Tests of the Liver; A Clinical Review\*

BY GEORGE B. EUSTERMAN, M.D., *Division of Medicine, Mayo Clinic,  
Rochester, Minnesota*

PROGRESS in our knowledge of the function and diseases of the liver has unfortunately been slow. With few exceptions it is only in recent years that intensive, coördinated effort on the part of the clinician, surgeon and research worker has begun to yield results of practical value. At long intervals in the past important contributions have been made by the anatomist, pathologist and physiologist, laying the foundation for some of our present conceptions and advances, but the sum total of indubitable facts has not been sufficient to make their application to the solution of our daily problems practicable. Cirrhotic changes, the result of a tuberculous, carcinomatous, syphilitic or extrahepatic obstructive process, are fairly well understood, but the classification of the other types of cirrhosis is still unsatisfactory.<sup>12</sup> In our ignorance as to their causes such classification is based on anatomic changes and functional disturbances which may be variously interpreted.<sup>11</sup> While we have always realized that the liver, like the spleen, suffers in silence, and that the former has un-

usual reserve and regenerative power, and is an organ of various metabolic, defensive and excretory functions (some of which until recently were not clearly understood), of its functional derangements we have been in the main blissfully ignorant.

Those who have had an opportunity to observe closely many cases, and have given much thought to the subject are impressed with our limitation in this field, and particularly with our inability always to differentiate the various types of jaundice and cirrhosis. Except perhaps in the field of pancreatic disease, exact knowledge bearing on etiology, diagnosis and prognosis leaves more to be desired than in most other departments of clinical medicine. Therefore, any procedure which gives promise of shedding light where there has been so much darkness should claim our sustained interest and encouragement.

In the last fifteen years investigations in various problems of research awakened scientific enthusiasm with regard to the biliary system. Chief among these are the results of physiologic research in which such investigators as Whipple, Blankenhorn, Rous, McMaster, Mann and his co-workers and Aschoff stand out; for example: investigations in the problems of dis-

\*Read before the Eleventh Annual Clinical Session of the American College of Physicians, Cleveland, Ohio, February 23, 1927.

sociated jaundice, especially those of the French school; studies concerning several recently recognized clinical varieties of jaundice; the formulation of a practical clinical classification of jaundice; Aschoff's contribution relative to the structure and important functions of the reticulo-endothelial system; extensive research directed to the function of the gallbladder; the elucidation of the pathogenesis of cholecystitis, hepatitis and biliary calculus; inquiries into the formation of urobilin and urobilinogen; the identification, chemical composition, and metabolism of the chief biliary constituents, bile pigment, cholesterol and the salts of bile acids; surgical advances in the treatment of certain diseases of the hematopoietic system in which the liver often participates; analysis of complications occurring in surgical lesions of the gallbladder and ducts which often implicate the liver, and in postoperative sequelae such as hepatic insufficiency,<sup>22</sup> and evolvement of biochemical methods to detect functional changes in disease of different organs, which resulted in the discovery of such familiar procedures as the van den Bergh test for serum bilirubin, the icterus index, and the Rosenthal test;<sup>17</sup> the latter had its origin in the researches of Rowntree, Horwitz and Bloomfield.<sup>17</sup>

It may be appropriate to call attention again to the fact that advances in medical science are often dependent on purely technical methods; the contrast-meal, the electrocardiogram and the cholecystogram are modern examples. While too much may have been claimed for the Lyon method of transduodenal biliary drainage from a

diagnostic and therapeutic standpoint, nevertheless this procedure has done as much or more to turn a flood of attention to the investigation of problems referable to the biliary tract than anything else. In this respect alone the method has served a useful and timely purpose and has therefore amply justified its existence.

#### THE MORE IMPORTANT FUNCTIONAL TESTS OF THE LIVER

Difficulties peculiar to the liver, with respect to study of its function, unlike those of the kidney, have been repeatedly emphasized in literature. Owing to various physiologic activities, a large number of tests have been devised as clinical indexes to functional changes in the organ. Many of them have already been discarded as of little, if any, value. Based on a combined clinical, experimental and pathologic study, the following have been found of major importance:

- I. *The van den Bergh test (direct and indirect reaction).*—This test determines the nature and amount of bile pigment in the serum. While the icterus index method is simpler, and preferred in many instances on that account, the van den Bergh test has the following advantages: (a) it distinguishes jaundice due to complete obstruction from hemolytic icterus; (b) it shows no deviation from the normal in cases of carotinemia, and (c) it lessens personal error in the reading, since one is less influenced by the variations in the color of the serum. The test is of primary importance in jaundiced patients, and is of greatest practical application in cases of obstructive jaundice. Moreover, it

furnishes a quantitative index for the degree of jaundice observed in the various toxic or infectious states, and it demonstrates the presence of latent icterus.

2. *The phenoltetrachlorophthalein or bromsulphthalein test of Rosenthal*—

This test has its greatest clinical value in cases of hepatic disease in which jaundice is not present; portal cirrhosis is a good example. In cases of jaundice the results parallel the bilirubin estimations, for icterus dominates the clinical picture and laboratory data. The dye test, in all probability, is only a measure of excretory function; a negative test, like a negative Wassermann test, does not exclude disease. Diffuse involvement is more likely to cause retention of the dye than a circumscribed lesion, and the amount of dye retained is not necessarily indicative of the degree of involvement. The test is not prognostic in a strict sense. The great reserve and regenerative capacity of the organ, together with the fact that disturbance of one function does not necessarily affect other functions, and the non-existence of any single test that is a measure of all the functions of the liver, are some of the reasons which delimit the value of all present functional tests.

3. *Bile salts in the blood and urine*.—Certain investigators regard the other two constituents of the bile, cholesterin and bile salts (cholates) of greater clinical importance than the pigment. The former is considered the major factor in the formation of biliary calculi, while the latter is believed to be the cause of such toxic

manifestations as pruritus, mental depression and bradycardia. The problem with regard to the bile salts, however, is not yet solved. A modified and standardized Pettenkofer test developed in the laboratories of the Mayo Clinic, although still imperfect, serves to indicate adequately relative changes in the bile salts of the blood.

Other tests, the nature and significance of which are more familiar, include determination of the coagulation time of the blood, fragility of the erythrocytes, and the amount and character of the bile and its products in the urine, stools and duodenal contents. Certain investigators in this field have ascribed to other procedures, especially to the estimation of urobilinogen in the freshly voided urine, a peculiar value.<sup>16-20-21</sup> Others again regard all functional tests as of limited value. But daily contact with cases of hepatic disease, and group investigations of the problems presented, convince us that the various tests with which we have familiarized ourselves, especially the dye and van den Bergh tests, are of considerable importance in diagnosis and treatment. They have at least served to stimulate a healthy interest in problems concerned with diseases of the liver and have made us realize our shortcomings in this field.

RESULTS OF FUNCTIONAL TESTS IN  
VARIOUS DISEASES OF THE LIVER

Several thousand van den Bergh and Rowntree-Rosenthal tests have been carefully carried out according to the technic described by Greene, Snell and Walters. Table 1 shows parallelism in the results of quantitative serum bilirubin estimations and

dye retention in cases of jaundice. It is only in those cases of disease of the liver or impairment of function without jaundice, that the dye test may be of value, such as portal cirrhosis, dissociation jaundice, metastasis to the liver, toxemia of pregnancy and hematemesia or melena provoked by latent or advanced cirrhosis of the liver.<sup>5</sup> In

significance if it shows increased values. In cases of cholecystic disease and jaundice, with 4 or 5 mg. of serum bilirubin, there is retention of dye. In such cases, cholecystography is of limited value, for the dye used in this test is closely related, chemically, to the dyes, ordinarily used for the test of hepatic function,

PETTENKOFER VALUE IN RELATION TO PRURITUS AND JAUNDICE IN LIVER DISEASE.

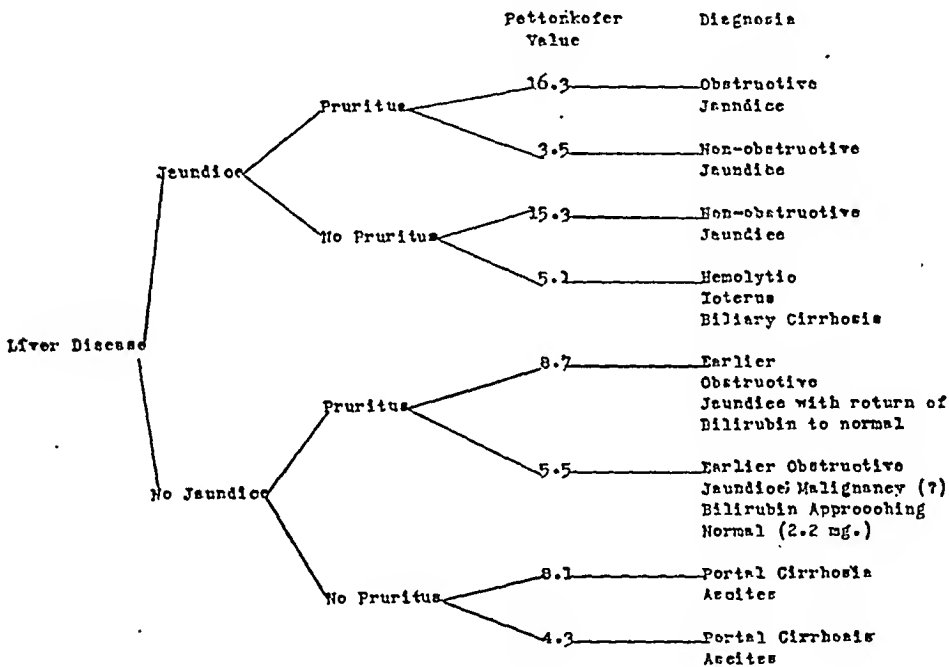


FIG. I

calculous or noncalculous cholecystitis both tests almost uniformly show normal values in the absence of jaundice. The associated hepatitis is undoubtedly too circumscribed to provoke functional changes. Therefore, the observations in the Mayo Clinic are not in accord with those of Laird, Brugh and Wilkerson, who would ascribe definite diagnostic value to functional studies in this condition. Of course the estimation of serum bilirubin following obscure abdominal colic may occasionally be of diagnostic

and therefore may be retained by the liver.

In the discussion of cirrhosis of the liver, two main groups are considered: (1) portal cirrhosis, with its clinical variations as regards size of the liver, presence or absence of ascites, and jaundice; the latter is seen only in the terminal stage of the disease, and (2) biliary cirrhosis as the result of extra-hepatic obstruction, and its absence; unlike the first group, jaundice is clinically the chief symptom, the liver is enlarged, and ascites is rare and

usually terminal. The spleen may be enlarged in either group. As stated, the dye test is of particular value in the diagnosis and study of cases of portal cirrhosis in which it is apparently an index to the existing functional balance between degenerative and reparative changes in the liver, which condition is largely independent of the amount of ascitic fluid present. While jaundice is not a striking manifestation in portal cirrhosis, estimations of serum bilirubin showed the presence of latent icterus in several cases. In all types of biliary cirrhosis such estimations have been particularly useful in ascertaining the degree of bile retention, which is uniformly present but is more marked than would usually be expected from the degree of bilirubinemia. This proportion is perhaps evidence of the pathologic changes in the liver. In the terminal stages of cirrhosis, irrespective of whether it is primarily portal or biliary, the clinical picture and pathologic and functional changes may be indistinguishable. Diagnostic differentiation, then, is mainly dependent on the history of the case, which includes in chronologic sequence all the details of remote events.

A clinical study embodying functional tests has been made in five cases of apparent dissociation jaundice by McVicar and Weir. This is a condition characterized by the presence of persistent pruritus, heretofore considered as due to an appreciable retention of bile salts without associated icterus, or without enough retention of pigment to be discernible in the skin or sclerotics. In several of these cases the symptoms and signs (icterus

and enlarged liver and spleen) were characteristic of biliary cirrhosis. The van den Bergh reaction in all cases was direct. The serum bilirubin in three of the cases was normal in amount, although abnormal qualitatively. In all the cases the dye retention was marked. Attention was called to the fact that in all unexplainable cases of generalized pruritus, hepatic function should be investigated. In some instances, 2 grains of calomel given daily in divided doses, two or three times a week, for a variable period, is effective in relieving pruritus. It was not conclusively shown that the pruritus was due to the presence of an increased amount of bile salts in the tissues. Rowntree, Greene and Aldrich have recently reported their results of quantitative Pettenkofer values in the blood based on several hundred determinations that have been carried out in the wards. The Pettenkofer value of normal blood varies from 2.5 to 6 mg. (in terms of glycolcholic acid) for each 100 c. c. Increased Pettenkofer values are frequently encountered clinically in hepatic disease. High values are most common in the presence of jaundice and in the earlier rather than the later stages of obstructive jaundice. High values may be found in cirrhosis of the liver in the absence of jaundice. Pruritus is commonly encountered in jaundice and is frequently associated with high Pettenkofer values. However, a direct causal relationship is lacking, since high values may persist over periods of weeks without pruritus, and itching in chronic disease of the liver may be marked when the Pettenkofer value is strictly normal.



With high Pettenkofer values, tachycardia or normal pulse rate is encountered more frequently than is bradycardia. The level of the Pettenkofer values does not seem to bear a direct causal relationship to decreased coagulability of the blood or to hemorrhage in cases of jaundice. Further clinical and experimental studies relating to the amount of bile acids in the blood and tissues, and the effects of their altered concentration on various physiologic functions, are in progress (Table 1).

My experience with tests of hepatic function in toxemia of pregnancy has been limited. Certain authorities believe that the pregnant state taxes hepatic function to the utmost.<sup>29</sup> Benda maintains that during the second half of pregnancy, and especially during labor, the reticulo-endothelial system is functionally impaired. King, Naujoks, and others, have reported their experiences with the van den Bergh and dye tests in this condition.

Functional changes in the liver are apparently not extensive enough to be of clinical significance in most diseases of the hematopoietic system (hemolytic jaundice, pernicious anemia, polycythemia, leukemia, and splenomegaly of the Gaucher type.<sup>8</sup> An increase in serum bilirubin is of value in the differential diagnosis of hemolytic anemia and the ordinary secondary types of anemia. The serum bilirubin is also an index in following the course of a hemolytic crisis after transfusion. The dye test may show changes in cases of splenic anemia, giving a clue to the severity of the cirrhotic process in the liver. The test would, then, seem to

be of some diagnostic and prognostic value. (Table 2.)

#### CERTAIN CLINICAL ASPECTS OF JAUNDICE

Since jaundice is the most striking single tangible sign of hepatic disease or dysfunction, a brief review of its salient features may not be amiss. McNee has classified jaundice into three main types, all of which have practical application. It is apparent that certain clinical types must be placed in two of the classifications; for example, cases of hemolytic jaundice with stone in the common duct, cases in which toxic changes in the hepatic cells or varying degrees of biliary cirrhosis are combined with definite obstruction of the extrahepatic bile ducts, whether due to stone or benign stricture. Leaving out of consideration those varieties of jaundice met with as a consequence of many acute infectious and protozoal diseases, or as the result of some definite toxic agent, there remains that large familiar group observed in daily practice that so frequently gives rise to difficulties in diagnosis. The majority of such cases, from a practical diagnostic and therapeutic standpoint, might be conveniently grouped into surgical, and nonsurgical types. In the former, as a rule, pain is an outstanding feature, the clinical course is usually characterized by recurrent attacks of pain, vomiting, and so forth, and the familiar associated symptoms are invariably coincident with the painful phenomena. The onset of carcinoma of the head of the pancreas is frequently painless and insidious, such as is seen in toxic or infectious types of jaundice. It must be remembered,

however, that this disease is not infrequently present in the absence of jaundice, especially in the earlier stages of the disease, and pain may be an early and predominant symptom, although usually it differs in character and degree from that of a stone in the common duct.<sup>4</sup> On the other hand, stone in the common duct may or may not be associated with the familiar colic, clay-colored stools, chills and rigor. The characteristic clinical symptoms and signs of both stone in the common duct and carcinoma of the head of the pancreas, as well as other entities, may frequently be atypical enough so that a differential diagnosis can only be made by careful study and observation of the patient in hospital, all available methods of diagnosis being applied at the same time. I believe that icterus as the result of disease confined to the gallbladder itself is usually transient, usually lasting about three or four days. Persistent jaundice complicating cholecystic disease is chiefly the result of an inflammatory, infectious or malignant process, usually affecting the extrahepatic ducts and, less frequently, the liver or pancreas. After operation on the biliary tract, the possibility of benign stricture as a cause of recurrent jaundice must always be considered. It is estimated that about one-third of the patients with such strictures give a history of typical biliary colic. In this connection emphasis must be placed on the injury to the vascular and biliary tree by long-standing obstruction of the common duct, which has been so well brought out by the studies of Counsellor and McIndoe. The severity of this injury is not sufficiently appre-

ciated by either the physician or the surgeon. The results of obstruction are most marked and rapid in cases of carcinoma of the head of the pancreas. In such conditions the serum bilirubin may be as high as 25 to 30 mg. for each 100 c. c. Low-grade, long-standing icterus in a youth or adult, without pruritus, with moderate enlargement of the spleen, and bile in the stool but none in the urine, all suggest the diagnosis of hemolytic icterus. In cases of recurring or protracted jaundice, associated with pruritus and pain, stone in the common duct, cholangitis, carcinoma of the head of the pancreas, chronic pancreatitis, and benign stricture should be considered as possibilities in the order mentioned: Carcinoma of the gallbladder, ducts, or papilla, and primary carcinoma of the liver are comparatively rare. It must be remembered that the commonest lesion in the liver is metastatic carcinoma which may have its origin in carcinoma of any organ situated in the peripheral portal system. In rare instances the metastasis to the liver is more in evidence than the original growth.

The nonsurgical or medical types of jaundice are largely of a toxic or infectious nature, intrahepatic in origin, and invariably painless. They may be associated with an enlarged, tender liver. Pruritus preceding painless jaundice by weeks or months is important diagnostically, as it suggests that the lesion producing the icterus is intrahepatic. Hemolytic forms of jaundice, whether of the acquired or congenital type, are also painless as a rule. It must be remembered, however, that in 58 per cent of such cases disease of the gallbladder is associated,

including pigment stones in the extra-hepatic ducts, in which event complicating factors are introduced.<sup>6</sup> In experienced hands, intrahepatic forms of jaundice can often be differentiated from obstructive types, and this obviates needless operations. Data derived from an examination of the bile, and estimation of pancreatic ferments obtained by single or repeated transduodenal biliary drainage are of diagnostic importance in this respect when taken in conjunction with other clinical evidence.

Jaundice that follows late after arsphenamine treatment must always be borne in mind.

In the physical examination special attention is paid to the size, consistency and form of the liver; palpability of the gallbladder; rigidity and tenderness over the right rectus; the presence of compensatory venous circulation on abdomen or back; the character, distribution and degree of jaundice, if present; determination of the presence or absence of ascites, metastasis, and purpuric areas; evidence of pruritus, and the gross appearance of the feces and urine.

In the last analysis a proper differential diagnosis depends mainly on time-honored clinical methods, including a complete history, with the appearance of the symptoms in chronologic order, and emphasis on the more important episodes, and a systematic physical examination, in addition to the routine examination of the urine and blood, including the determination of coagulation time, and fragility tests.

#### TREATMENT OF DISEASES OF THE LIVER

A wider understanding of the liver and its diseases should result in more

effective treatment. It should affect the principle of medical management, increase one's ability to determine the degree of surgical risk and improve surgical judgment and surgical results. Encouraging progress has been made, especially in the preoperative preparation of the jaundiced patient, in removing and controlling ascites of portal cirrhosis and in the treatment of the toxemias associated with hepatic insufficiency. A condensed but inclusive outline prepared by Rowntree, is as follows:

*Prevention.*—Care of acute infections and chronic foci, especially intra-abdominal foci; care relative to the use of alcohol, condiments, chloroform, arsenic, phosphorus, copper, phenylhydrazin, and tar, and care in industry with phosphorus, "aëroplane dope", and picric acid.

*Treatment.*—Constitutional specifics: arsphenamine, iodide, mercury, emetin, quinine, and vermicides. Hepatic specifics: water, glucose, and calcium.

*Functional restoration.*—Relief of biliary obstruction: transduodenal biliary drainage. Relief of portal obstruction: Talma-Morrison operation, splenectomy, paracentesis, the administration of merbaphen, and ammonium salts, and restriction of salt and water. Hemolysis: splenectomy. Congestion: digitalis, diuretics, and restriction of salt and water. Protection from hemorrhage in jaundice: calcium chloride, transfusion, carbohydrates and water. Symptomatic relief of pruritus: calomel, emetin, diathermy, and sweating. Relief of gastro-intestinal disturbances: diet and sedatives.

TABLE 1  
*Illustrative cases*

DISEASE	Phenoltetrachlor- phthalein retention after one hour, per cent	Serum bilirubin, mg.
Obstructive jaundice .....	3.0*	1.0*
Carcinoma of head of pancreas with obstruction.....	30.0	25.0
Metastatic carcinoma of liver with icterus.....	36.0	35.7
Infectious jaundice .....	28.0	36.2
Toxic jaundice and pneumonia.....	25.0	17.3
Syphilitic hepatitis with jaundice.....	15.0	8.7
Myocardial insufficiency and jaundice.....	26.0	13.1
Toxic jaundice with exophthalmic goiter.....	30.0	12.7
Metastatic carcinoma of liver.....	22.0	20.4
Biliary cirrhosis .....	22.0	2.4
Atrophic cirrhosis .....	17.0	2.6
Toxemia of pregnancy.....	8.0	1.0
Carcinoma of stomach without metastasis.....	8.0	0.5
Chronic cholecystitis .....	2.0	1.0
	2.0	1.4

\*Normal person.

TABLE 2  
*Results of functional tests in various diseases of the liver*

	Cases	BILIRUBIN			BROM- SULPHALEIN			BILE ACIDS		
		Minimum, mg.	Maximum, per cent	Positive	Minimum, mg.	Maximum, per cent	Positive	Minimum, mg.	Maximum, per cent	Positive
Normals										
Laboratory workers .....	40	0.2	1.0	0	0	2	0	2.6	5.1	0
Hospital patients .....	70	0.2	1.8	0	0	10	0	2.6	5.2	0
Chronic cholecystitis .....	40	0.2	1.9	0	0	30	8	3.0	5.7	0
Obstructive jaundice										
Common duct stone.....	14	2.4	12.8	14	20	60	14	3.4	8.8	6
Stricture of duct.....	15	1.2	9.1	9	10	60	15	3.7	10.4	2
Tumor of pancreas.....	8	10.2	33.4	8	14	96	8	3.0	19.8	5
Carcinoma										
No hepatic involvement.....	14	0.2	0.9	0	1	12	2	3.0	3.8	0
Metastasis, no jaundice.....	36	0.2	5.8	2	2	72	31	2.0	8.0	6
Metastasis and jaundice.....	6	3.0	39.6	6	40	64	6	4.1	16.5	3
Hemolytic jaundice .....	16	2.9	8.7		0	8		3.1	6.2	1
Pernicious anemia .....	8	0.8	4.6		0	8		5.3	6.2	1
Splenic anemia .....	20	0.2	2.8	2	0	60	15	3.4	6.2	1
Myocardial failure with passive congestion .....	30	0.2	4.5	2	8	64	25	2.7	5.4	0
Hypertension .....	16	0.2	1.7	0	0	8	0	3.2	5.7	0
Portal cirrhosis										
Small liver .....	16	0.6	2.2	3	6	60	14	3.9	8.1	2
Large liver .....	20	0.6	3.1	7	5	64	18	3.8	7.2	3
Biliary cirrhosis										
Obstructive type .....	11	1.2	7.3	7	20	44	11	2.7	14.3	4
Nonobstructive type .....	9	1.6	17.8	7	24	56	9	5.0	8.0	3

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# Results of Liver Function Tests\*

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**D**URING the past three years much has been said and written about liver function tests. While everyone who has worked with the various tests feels that these laboratory examinations add some information to the understanding of liver disturbances, as yet no final statement has been made as to their value in the observation and diagnosis of diseases of the liver. The correlation of laboratory findings and the clinical picture presented by the individual case has been difficult, and we feel that it is only by extensive observations that such correlations will be obtained. In order to gain first-hand information in our own cases, as well as to add to the data being accumulated on this subject, somewhat less than a year ago we began to carry out the several liver function tests in cases in which an impairment of the liver was either obviously present or was suspected. The purpose of this paper is to report the results of some of these studies.

We have used the bromsulphthalein dye test; the levulose tolerance test; and both the van den Bergh and the icterus index tests in the estimation of the serum bilirubin. The Widal

hemoclastic crisis test was not used because the time and the technique necessary for securing accurate data make it unsuitable for clinic study. In the hands of some observers, however, the Widal reaction test has proved to be of distinct value, and perhaps in the future we shall find it necessary to add this test to our study of disease of the liver.

The levulose tolerance test has proved to be of little value in the early stages of liver disease, and even in late stages it gives very slight evidence of the lowering of tolerance. It is probable that in the function of conversion of fructose to glucose the liver has an extremely large factor of safety. Most of our data, therefore, have been acquired by the use of the bromsulphthalein dye test and by the estimation of serum bilirubin. Bromsulphthalein is the only dye we have used during the past ten months. Some few years ago phenoltetrachlorphthalein was tried, but early in our experience we met with an unfortunate accident—thrombosis of the femoral vein following the intravenous administration of the dye in the arm. The dye tests were discontinued at that time until Rosenthal brought out the newer dye, bromsulphthalein. This dye is a distinct improvement over former reagents, as it fulfills almost all the

\*Clinical discussion given before the American College of Physicians at the Cleveland Clinic, February 22-25, 1927.

requirements for a perfect testing agent. First, it is nontoxic even in rather large doses—we have never seen evidence of thrombosis and we have used it in over 80 cases. Second, it is taken up entirely by the liver, practically none being excreted by the kidneys. In this respect also it is better than phenoltetrachlorophthalein. Third, the time required for the test is short, thirty-five to forty minutes being sufficient, a feature which is obviously important in dealing with non-hospitalized cases. We feel, therefore, that bromsulphthalein is distinctly the reagent of choice in dye tests for liver function.

It is not necessary to give the details of the technique of this test; the procedure is quite simple and is well described in Rosenthal's original article. I wish merely to emphasize its value in the observation and diagnosis of liver disturbances.

As I said before, we have made 80 examinations in 63 individuals. Among these 63 cases, 31 showed retention of dye, the degree of retention ranging from five to 70 per cent. In order to correlate these findings with the clinical diagnoses it seems expedient to separate the cases into two groups, those in which jaundice was minimal or absent, and those in which jaundice was moderate or extreme. In 17 of the 31 cases there was a low serum bilirubin in the presence of a retention of from five to 30 per cent of the dye. Of these 17 cases, in 13, or 76 per cent, the clinical diagnosis of cirrhosis had been made; and in three, chronic passive congestion due to myocardial failure was present. On the other hand, of the 32 cases in which there was no dye retention, in only one was there clinical

evidence of early cirrhosis. It is evident, therefore, that the dye test may well be of distinct service in indicating the differential diagnosis in cases in which cirrhosis is suspected but icterus is not present. In fact, it is in cases of liver disease without marked jaundice that the dye test is most useful.

In cases in which the jaundice is very definite or marked, however, the use of the dye test adds little to the clinical data, as the degree of retention parallels closely the degree of jaundice. In cases of obstructive and catarrhal jaundice with a serum bilirubin of from six to 15 mgs. per 100 cc. there was a retention of from 35 to 70 per cent, while in cases of metastatic carcinoma of the liver with a serum bilirubin of five mgs. or less, the retention was only 20 per cent. This variation in the degree of retention might be of possible benefit in establishing a differential diagnosis, but nevertheless we feel that the chief value of the bromsulphthalein dye test is in cases in which there is no jaundice.

In discussing the determination of serum bilirubin, whether by the van den Bergh or the icterus index method, I wish not so much to prove the value of these determinations—a well established fact—but rather to point out a few of the interesting uses to which they can be put. Jaundice, whether apparent or subclinical, is classified as obstructive, hepatic, and hemolytic. By the use of the van den Bergh reaction hemolytic jaundice can be differentiated from jaundice of the hepatic or obstructive type. It is also believed that a biphasic or delayed reaction indicates that the icterus is hepatic in origin. This point has not

Form 173

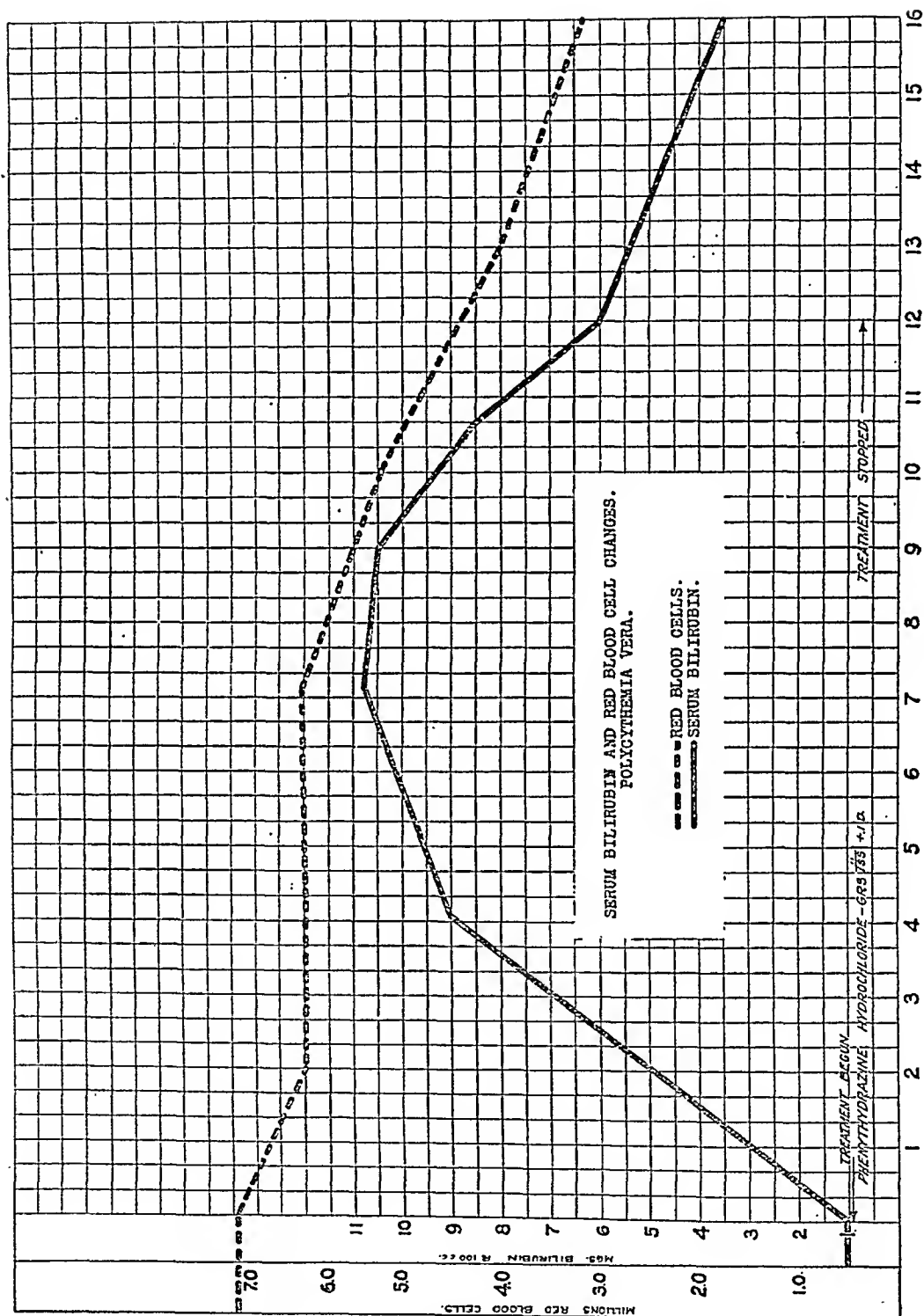
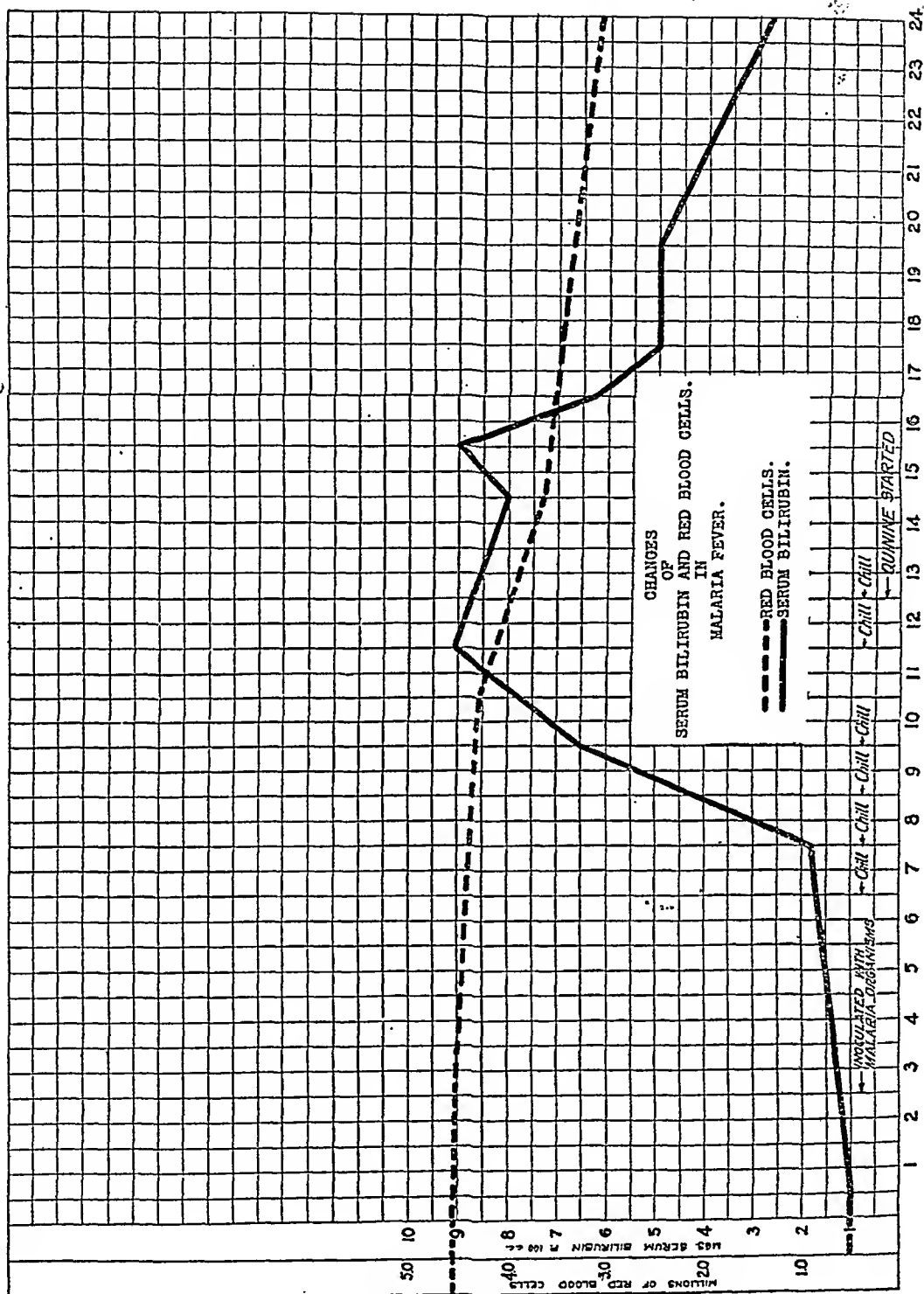


Chart I



Form 179



## Chart II

been entirely proved but it is well known that in catarrhal jaundice the bilirubin test gives this type of reaction.

Determinations of the serum bilirubin are definitely of value in following the progress of patients from day to day. This subject has been much stressed, especially by surgeons, who regard the study of the degree of jaundice and its changes as a most necessary factor in the treatment of obstruction of the common duct. From the medical standpoint the study of diseases by this means is also illuminating, and controls in certain instances the course of treatment. The accompanying charts illustrate the findings in successive bilirubin tests in the course of two of the cases in our series.

Chart I illustrates the changes in the serum bilirubin and red blood cell counts in a case of polycythemia vera under treatment with phenylhydrazine hydrochlorid. It will be noted that soon after the treatment is started the serum bilirubin rises rapidly—much more rapidly than the red cell count decreases. It is probable that the circulating red cells are maintained by mobilization of cells from the bone marrow. The van den Bergh reaction is always indirect, showing the hemolytic origin of the bilirubin. This has been very convincing in proving to me that there are two kinds of bilirubin. I have always suspected that the indirect reaction was due to a combination of bilirubin with cholesterol or adsorption in the serum proteins. However, this amount of bilirubin is equivalent to that seen in marked jaundice with obstruction and therefore it shows that the amount of bilirubin is not a factor in the direct and indirect reactions. A

clue is also given as to the length of time treatment should be continued. In this case an anemia of 2,500,000 red cells developed, the fall in the cell count continuing for a week or more after the discontinuance of the treatment. No doubt the treatment ought to have been stopped when the maximum blood cell destruction was reached, as indicated by the serum bilirubin.

Chart II illustrates the changes in the bilirubin and red blood cell counts in a case of malarial fever which had been produced in the treatment of general paresis. The chills on successive days are also indicated. This patient became quite ill and because of the marked elevation of the serum bilirubin, the chills were terminated by quinin. The reactions in this case were biphasic and indirect. That is, some color was produced gradually before the addition of alcohol but it was markedly increased by alcohol. Clinically this patient showed evidence of liver disturbance which was probably due to the malarial fever.

Such data add interest to the study of such conditions and in many cases prove of real value in determining the type of treatment which should be employed.

#### CONCLUSIONS

1. The levulose tolerance test is of slight value in the study of liver diseases.
2. The bromsulphthalein dye test is of distinct value in the diagnosis of liver disturbance, especially in the absence of jaundice.
3. The van den Bergh reaction is valuable in the differential diagnosis of conditions in which icterus is present and in following the course of the disease in such cases.

# Urobilin Physiology and Pathology\*

(ABSTRACT)

By PHILIP D. McMASTER, M.D., AND ROBERT ELMAN, M.D., *New York*†

**C**LINICAL interest in urobilin has always been great, yet at the present day the conclusions confidently drawn by workers with the substance far outrun actual knowledge of it. Analysis of the previous literature makes clear that the hypotheses of the origin of this pigment show no semblance of accord (1, 2). Every conceivable organ and tissue has been championed by one author or another as the sole site of origin of urobilin.

In the course of studies upon the physiology of bile made in this laboratory, methods were described (3, 4) whereby animals can be totally, partially and intermittently deprived of their bile without infection of this secretion or of the duct system. These methods possess obvious advantages for the study of urobilin physiology since they permit a comparison of the effects of total and partial bile loss upon the formation of this pigment. It will be seen too that the absolute exclusion of bile from the intestine, which one of these methods affords,

is necessary to any such study. Our work has been carried out with healthy, robust animals having uninfected livers and bile passages, save in a few instances to be mentioned, in which deliberate infection was accomplished for purposes of comparison.

Means were also found (5) to avoid the influence of the factors responsible in part for the inaccuracy of urobilin determinations through the development of clear fluorescent solutions from urobilin-containing urine, feces, and bile obtained from the dog. Conversion of the urobilinogen to urobilin was accomplished during the procedures. Measurement of the urobilin content was effected by comparing its fluorescence at great dilution with a standard containing acriflavine, calibrated in turn against pure urobilin.

Though designed for experimental procedures on the dog, the methods would seem adapted for clinical uses as well. With these aids we have studied urobilin physiology.

## DERIVATION OF UROBILIN. RELATION OF THE BILE TO THE PRESENCE OF UROBILIN IN THE BODY

We have been able to show that the normal presence of urobilin in the bile

\*Presented at the Cleveland Clinical Week of the American College of Physicians, February 23, 1927.

†From the Laboratories of the Rockefeller Institute for Medical Research.

and feces of dogs depends on the passage of bile pigment to the intestine, either through the normal channels, or by abnormal ones, as when it is fed by mouth (4). Complete loss of the bile from the body resulted in the total disappearance of urobilin and urobilinogen from the bile, feces, and urine. Rarely very faint traces remained in the feces, the origin of which was discussed. Partial loss of the bile resulted in a corresponding reduction in the urobilin of the dejecta (4).

Total obstruction of the bile flow caused disappearance of the urobilin of the bile and stool (4). Later as the animals became heavily jaundiced the pigment appeared again in very small quantity in the feces. Autopsy at this time showed that the intestinal mucosa was deeply tinted with bilirubin some of which had undoubtedly passed into the lumen of the bowel and had there been changed to urobilin.

Employment of the "altercursive intubation" (4), by which an intermittent diversion of the bile stream of animals from the intestine to a collecting apparatus could be effected, showed that while bile pigment still reached the intestine urobilin was present in the bile secreted by the liver but that almost at once after the bile had been diverted from the gut urobilin disappeared from it. In relation to this finding it was noticed that in animals from which merely a small fraction of the bile was collected, that from a single liver lobe, while the greater portion reached the intestine there was most urobilin in the bile at

times when most bilirubin was entering the intestine.

The earlier work of others has established the fact that urobilin can be obtained from bilirubin, *in vitro*, by reduction (6, 7). That this change takes place in the intestine as well, by the action of bacteria, has also long been known. In recent years (8) experiments upon the method whereby this ordinarily comes about in man have shown that certain of the intestinal flora possess this transforming ability. These factors account for the presence of urobilin in the stool—but what of its presence in the bile?

#### ABSORPTION OF PIGMENTS OF BILIARY DERIVATION FROM THE INTESTINE

In the course of these studies, dogs losing the total bile as the result of common duct intubation, and in consequence urobilin-free—the bile, feces, and urine containing none of the pigment—were fed either their own bile or urobilin-free bile from similar urobilin-free dogs. All the animals so fed exhibited a great increase of the bilirubin of the bile and urobilin appeared in it (4). From this fact and from others it became evident that urobilin appeared in the normal bile only when bile pigment in some form was allowed to reach the intestinal tract. The evidence pointed to the absorption from the intestine either of the pigment or of substances out of which it might be formed. A closer study of the problem of this absorption has been undertaken. For the purpose pure bilirubin and urobilin have been used and the total bile collected from day to day in a sterile condition

according to the methods mentioned above (3, 4).

Feedings of pure bilirubin by mouth to dogs, like those of whole bile, increase greatly the amount of this pigment in the hepatic bile (9). Control feedings of bile salts, while greatly increasing the bile quantity, cause no change in the pigment output. Instillations of pure bilirubin directly into the duodenum of dogs, appropriately intubated, are followed by pronounced increases in the bilirubin output in the bile (9).

Feedings of pure urobilin to dogs, yielding urobilin-free bile, as result of diversion of the secretion from the intestine, are followed by the appearance of this pigment in the bile (9).

The phenomenon of pigment reabsorption would appear to be far-reaching in its implications. It must be taken into account in any hypothesis of pigment metabolism. The clinical utilization of the urobilin output in the feces as a measure of blood destruction should only be undertaken with the understanding that urobilin is subject, not only to degradation but to reabsorption.

#### THE FORMATION OF UROBILIN UNDER PATHOLOGICAL CONDITIONS

These experiments have yielded answers to a number of questions of prime importance in urobilin physiology. Together they prove that the existence of urobilin in the stool, and in the bile as well, under normal conditions depends on a delivery of the bile itself, or, to speak more precisely, of bilirubin to the intestine. Here it is changed to urobilin, and thence re-

absorbed in part, to be taken out of circulation again by the liver and partly, at least, secreted into the bile.

*Urobilin and the Damaged Liver.* A variety of evidence was presented (10) showing that these facts hold true even under circumstances of severe liver damage or biliary obstruction when unaccompanied by infection. Animals rendered urobilin-free by collection of all the bile from the intubated common duct remain urobilin-free after severe hepatic injury by chloroform, phosphorus, toluylene-diamine and amyl alcohol (10), even when severe enough to cause death.

In our experiments urobilinuria was never found after liver damage except when bile pigment was present in the intestine. Thus, for example, it appeared during the first days after ligation of the common duct, but disappeared as the stools became acholic. When this had happened a small amount of urobilin-free bile, given by mouth, precipitated a prompt urobilinuria. After obstruction of the duct from one-third of the liver, mild urobilinuria was found, but no bilirubinuria. In animals intubated for the collection of a part of the bile only, while the rest flowed to the duodenum through the ordinary channels, liver injury caused urobilinuria, unless indeed it was so severe as to lead to bile suppression, when almost at once the urobilinuria ceased, though the organism became jaundiced (10).

The evidence here presented, when taken with that of our previous papers (4, 9, 10, 11), clearly proves that urobilinuria is an expression of the inability of the liver cells to remove from circulation the urobilin brought

by the portal stream, with the result that the pigment passes on to kidney and urine. Urobilinuria occurs with a far less degree of liver injury than does bilirubinuria.

*The Relation between Urobilin and Conditions Involving Increased Red Blood Cell Destruction*

Further evidence was presented (II) that the intestinal tract is, under ordinary circumstances, the sole place of origin of urobilin.

Animals rendered urobilin-free by the collection of all the bile from the intubated, uninfected common duct, remain urobilin-free during and after extensive blood destruction caused by intravenous injections of distilled water, as also after reinjections of the animal's own blood, hemolyzed *in vitro*. No urobilin appears in the bile, urine, or feces of animals so intubated when blood destruction has been caused by sodium oleate, or by an agent, toluylenediamine, which damages the liver as well as the blood (II).

On the other hand, when bile flow into the intestine is uninterrupted, urobilinuria occurs during blood destruction caused in any of the ways mentioned and it parallels, both in severity and duration, the destructive process. (II).

Merely increasing the amount of bilirubin within the intestines of healthy dogs by feeding urobilin-free bile, will lead to marked urobilinuria (II). The extravasation of blood into the tissues, resulting from the trauma of an operation for intubation of a bile duct, does not lead to urobilinuria in animals losing all of the

bile after this operation, but may do so when only a small fraction of the bile is drained, while the remainder reaches the intestine as usual. The production of artificial hematomas, without operation, is not followed by urobilinuria, under the circumstances last mentioned, but merely by an increase in the bilirubin of the bile. The effect on the liver of the anesthetic employed during the intubation may be responsible for the difference in the two cases (II).

During the course of certain intercurrent infections affecting some of the intubated animals, notably distemper, there was a drop in the hemoglobin percentage of the circulating blood, accompanied by an increased output of bile pigment or further by urobilinuria, when the conditions were such that bile still reached the intestine. The findings pointed to increased blood destruction as a factor in the urobilinuria.

The evidence presented suffices to demonstrate, that urobilinuria, occurring during blood destruction, is primarily the result of an increased excretion of bilirubin from which, in turn, an unusually large quantity of urobilin is formed within the intestine. The liver fails to remove from the portal blood all of the latter pigment which is resorbed and consequently some of it reaches the kidneys and urine.

THE RELATION OF BILIARY INFECTIONS  
TO THE GENESIS AND EXCRETION  
OF UROBILIN

The evidence thus far assembled was obtained from the study of animals with uninfected livers, yielding sterile bile. How will the infection of

the liver with urobilin-producing bacteria affect our conclusions? That one may actually produce urobilin *in vitro* by inoculating sterile urobilin-free bile is well known (6, 7, 8). We have been able to accomplish the same thing *in vivo*, for the experimental infection of the intubated and previously sterile biliary tract of the dog with particles of the stools leads to a formation of urobilin from the bilirubin of the bile as it flows through the ducts (12). No urobilinuria occurs, however, unless temporary biliary obstruction is produced, or the liver parenchyma injured. Then urobilinuria develops, despite the fact that no bile is reaching the intestine and, by corollary, no urobilin being formed there.

Cholangitic urobilinuria, as one may term the phenomenon just described, to distinguish it from the urobilinuria having origin in pigment absorbed from within the intestine, is far more pronounced in animals possessing a healthy gall bladder than in those with a pathological gall bladder or with one prevented from functioning by severance of the cystic duct (12). These facts suggest that there may be an active absorption of urobilin from the normal gall bladder. There can be no doubt that the pigment is absorbed from within the bile ducts.

The experiments here described throw light upon the mechanism of a type of urobilinuria previously considered due to the formation of urobilin from the liver cells. Instead of invoking such a parenchymal activity—for which our extensive experiments already reported yield not the slightest evidence—it is now possible to explain

the observed facts by the absorption of urobilin produced through bacterial action on the bile passing through ducts and gall bladder. The possibility that urobilin formed in this way, in an infected biliary tract, may be reabsorbed therefrom and excreted in the urine constitutes, theoretically at least, an extraintestinal origin of urobilinuria. But it must be clearly pointed out that the phenomenon, if it occurs in man, is extraneous, having nothing to do with liver function or with urobilin physiology as such, no matter how important it may be clinically.

The experimentally induced formation of urobilin in an infected biliary tract gives a ready explanation of certain discrepancies between our findings and those of others. In all previous experiments of this nature an open, infected fistula has been present, one infected doubtless with organisms capable of producing urobilin in the bile. Such organisms are present in dog feces and the animal usually has access to the fistula opening. We believe that all of the instances of the supposed hepatic formation of urobilin may be explained in this way.

The fact should be emphasized that only a certain type of infection will bring about the changes described. The biliary tract may be infected for a long time with the ordinary saprophytes or even with pyogenic organisms without any reduction of the bilirubin to urobilin. Some fecal bacteria by contrast are capable of maintaining themselves in the biliary passages for indefinite periods of time, there causing urobilin formation. That some of the urobilin is absorbed our experiments show. The question

whether a manufacture of urobilin ever takes place within the biliary tract of human beings other than those having biliary fistulas is one of much clinical importance. A bacteriological study of infected biliary tracts should be undertaken by surgical pathologists with a view to determining the incidence of urobilin-producing organisms.

There is no evidence whatever to justify the belief that urobilin is ever formed through the action of liver parenchyma. There may conceivably be an intralobular formation of the pigment consequent upon the activity

of bacteria within the liver tissue, though such a happening has yet to be demonstrated.

The fact is to be emphasized that urobilin appears only when the bilirubin of the bile is subjected to reduction by certain bacteria. Normally this takes place in the intestine but it may also occur in a biliary tract contaminated with the appropriate organisms. Urobilin in the urine depends, first upon the absorption of the substance from these situations, and secondly, upon the failure of the liver to remove the pigment from the blood.

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# The Clinical Significance of Jaundice\*

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THEORIES in the matter of jaundice and ideas, coming from the laboratory or the bedside, that contemplate the physiology and the pathology of bile pigment as anything other than an affair of the liver have never gone far in useful application. Stoppage of the gall ducts or gross abnormalities of the liver are so commonly the cause of jaundice that the liver and its ducts have always been the principal consideration when jaundice is to be explained.

Virchow's (1) demonstration that a strange pigment which forms about extravasations of blood was identical with the bile pigment gave rise to a theory that bile pigment could be formed outside of the liver. This knowledge together with the clinical observation on the relation between anaemia and jaundice gave rise to the old classification into hematogenous and hepatogenous jaundice. A classification useful only so far as it can be applied, but never very useful any more than to say that in the former type the liver is excluded—while in the latter the liver is involved. Minowski and Naunyn's (2) famous experiment with the goose stood for

many years as the final and conclusive proof that without the liver there could be no jaundice—yet clinical medicine was little influenced by the apparent conflict between experimental fact and clinical fancy. The goose experiment in fact seemed incontrovertible and was never repeated until very modern times, and after the birth of the so-called reticulo-endothelial system, when McNee explained the discrepancy by showing that removing the liver from the goose likewise removes the bulk of the reticulo-endothelial system in that particular animal. Eppinger's (3) all inclusive theory that all jaundice is due to bile thrombi in the liver likewise had no profound influence in our clinical thinking, although it endured as a theory for a long time. Present day practice—even "up to the minute medicine"—still deals mostly with the old-fashioned ideas although remarkable new facts are at hand as to the physiology of bile pigment formation and new laboratory technique for the study of jaundice. Chief of the newer methods is the examination of blood for bile pigment—whether it is done by methods of direct comparison as with the Mühlengracht (4) standard or by the Van den Bergh (5) method it is a simple device. The simple un-

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adorned statement of the bilirubin content of the blood will always be useful because it is evidence of an abnormal process. When the Van den Bergh method is used only as a measure it serves a good purpose even though difficult to do, but when the so-called Van den Bergh tests are used to tell us the cause of the jaundice we revert to necromancy, and the reading of oracles.

McNee (6) has recently offered us a rationale for these Van den Bergh tests, and has tried to make them reputable by proposing a theory. The theory begins with the fact that bile pigment is formed outside the liver in the reticulo-endothelial system, and that the epithelium of the liver constitutes a filter membrane with the pigment, born in the bone marrow, spleen and elsewhere on the giving side, and the bile capillary on the receiving side. It regards also the three varieties of Van den Bergh tests—direct, indirect and biphasic, and the well-known orthodox—three kinds of jaundice, that in which the liver is obstructed called hepatogenous, that in which the liver is not obstructed called hematomogenous, and unknown forms. The theory assembles all these facts into a homogeneous whole according to a uniform principle as follows—that the direct test is due to bile pigment that has passed through the liver filter and is then reabsorbed, and that the indirect test is due to pigment that has never passed the liver filter, and that the biphasic is due to the both forms combined. Any theory true or false is a good one if it inspires thought and compels work, but this theory of jaun-

dice is a bad one because it leads not at all to thinking or working, but only to the reading of tests. It is doubly bad because the tests do not work. But because these tests are convenient and are backed up by a plausible theory they have taken well in medical practice. The most recent edition of the Osler has given undue prominence to these tests so that the old-fashioned methods of study are slighted. Something should be done about it. This much has been done. Medical literature, particularly that dealing in case reports, frequently shows where the tests have been applied and the experienced clinician has been led seriously astray. These reports are numerous, but too scattered to be cited here. However, the situation is confusing and merits more critical view of the heart of the matter—that is, the experimental basis and reason for the tests. I feel such a discussion is in order here.

Van den Bergh's original observation that there are three kinds of tests—direct, indirect and biphasic—has given rise to the idea that there are three kinds of bile pigment in the blood, as the manifestation of three separate pathological processes. The Van den Bergh test, if you permit me to remind you, is a color reaction between Ehrlich's diazo reagent and bilirubin. That bilirubin reacts in a specific way to develop this color no one has disproved, nor even reasonably denied. It is affirmed that with three different tests we have proved three different substances, but the indirect test you may recall is done exactly like the direct excepting that the blood

plasma is treated first with alcohol in order to develop color.

It is my belief based on experimental work of my own (7) and reported in 1919 under the title "Acholuric Jaundice" that we are dealing in this situation—not with three separate substances, but with in one instance, bile pigment in simple solution in the blood, in another instance with bile pigment adsorbed to the blood protein and in the third instance with mixtures of the two. I came to this conclusion by finding that bile pigment in simple solution passes the kidney filter into the urine and can be made to dialyse from the blood. I have found further that bile pigment which was attached to the protein would not dialyse from the blood and would not pass the kidney filter. I found also that there were mixtures in which there was bile pigment in simple solution and bile pigment adsorbed to the protein in varying amounts. I made further observations that in haemogenous jaundice there was no bile pigment in simple solution, but there was much attached to the protein and consequently none in the urine. I found further that in obstructive jaundice that there was much bile pigment in simple solution, that there was little bile pigment attached to the protein, and therefore much bile pigment in the urine. I supposed then that we were dealing here with different substances and that the study of such findings might lead to the analysis of the more difficult clinical problems. In the end, after applying dialysis to many clinical specimens, I came to the conclusion that the degree of adsorp-

tion of bile pigment to protein was not dependent on the pathogenesis of the jaundice, but dependent on purely physical—possibly on physical chemical factors—in the main dependent on those things which modify the absorption of the dye to colloidal substances. To be more exact when bile pigment is dosed into the blood stream rapidly and in large amounts there is much in simple solution and little adsorption to protein, and when bile pigment is dosed into the blood in small amounts and over a long period of time, there is little or none in simple solution, but there is much attached to the protein. In the end, so that instead of giving evidence to the origin of different varieties of bile pigment, I find evidence pointing to the rate and the duration of the staining of the body with a dye. These clinical observations I was able to augment by *in vitro* experiments with protein and with dye in which I was able to reproduce specimens produced by my patients. Later on with the advent of the literature on the Van den Bergh tests, I found that bile pigment in simple solution in the blood gives a direct test, bile pigment attached to the protein gives indirect test, and that mixtures give the biphasic. I am by no means alone in this idea, nor do I claim priority.

Rich (8) dealing with combination of bile pigment and protein which gives only the Van den Bergh indirect has exposed the blood to a proteolytic enzyme and thereby transformed the indirect to the direct. This experiment I have done myself and, furthermore, have incubated mixtures of pig-

ment and protein so that I have transformed the Van den Bergh direct into the Van den Bergh indirect—more than this Favilli (9) has ligated the common duct of dogs, rabbits, guinea pigs and has found that in this situation the Van den Bergh has passed gradually from the indirect to the direct—sometimes all three forms being present at once. He concludes that the three tests are due to varying degrees of adsorption of bilirubin to protein. Oka T. (10) has done the same thing and came to the same conclusion. Levi and Crailsheim (11) did the same. Rosenthal (12) has gone farther on the same theory and has studied the relation of bile salts to the process of adsorption of dye to protein. He would add the influence of bile salts as another factor in determining the relation of pigment to protein. My own efforts were able to describe only two factors—that is the time and the intensity of the staining process. It is, therefore, timely to point out, from practical considerations as well as critical experimental studies, that the Van den Bergh tests can not answer our questions as to the cause of jaundice. What have we that is any better? Let us see what jaundice means today. The latest work on the formation of bilirubin by Mann (13) and his associates shows very satisfactorily that some other structure than the epithelium of the liver is responsible for the origin of bilirubin. He has gone further and shown that the spleen and bone-marrow—in fact all of the tissues of the reticulo-endothelial system, form bile pigment in considerable amounts. Whether they have shown

that bile pigment is not formed by the Kupffer cell of the liver is unimportant. We can safely say with Mann that bile pigment is formed by the reticulo-endothelial system. Farther than this it is unwise to go. Rich has shown to our satisfaction that there is no other source for bilirubin than destruction of the red cell and liberation of hemoglobin. The theory that all bile pigment is formed outside of the liver epithelium, and that the liver epithelium is the organ of excretion, can be readily accepted and harmonized with all of our clinical experiences to date. This theory can be pushed to its logical conclusion. We can consider jaundice then as a reaction between a dye substance and the colloids and water of the body. Ordinarily this dye substance is eliminated by way of the liver, but there is a normal amount always present in the blood. This amount is variable in individuals and fluctuates with the taking of food—being increased by fasting and diminished by digestion. By definition this normal amount never increases to the point of becoming jaundice. Precisely how in any instance this normal pigment becomes increased to the degree of being visible as jaundice is not known and need not be known. We can, without further theorizing, estimate the amount of bile pigment in blood, in urine and stool, in many simple cases of jaundice and from that hope to understand the more complex problem. The most satisfactory method for the blood is the direct comparison with an artificial standard of potassium dichromate — after Meulengracht. Carotin

is the only substance that seriously interferes with this method, but carotin jaundice is easily disposed of by being recognized by its distribution in the body. Carotin stains mostly the thick skin of the palms and soles, and does not stain the sclerae—while bilirubin icterus does just the opposite. Urobilin is not a colorful substance and causes no jaundice. Bile pigment in the stool is present usually only as urobilin and the method of McMaster (14) or that of Wilber and Addis (15) is satisfactory. The urobilin content of the stool is a good guide to the bilirubin output of the liver. Urine can be measured by the method of Whipple and Hooper (16) and results are accurate enough for comparison in well conducted case study. It is true that these laboratory methods are troublesome, but the end results are useful. They have this virtue in that they are of the staining process known as jaundice—they are not tests applied to seek out certain disease entities. With this method of study it is perfectly obvious that patients with obstructive jaundice have increasing amounts of bile in the blood and urine, but none in the stool. It is obvious that patients with so-called hemogenous jaundice have much bile in the blood—much bile in the stool and little or none in the urine. When sufficient number of cases of jaundice that can be acceptably classified are studied so that we understand them and know what to expect as to the amount of bile pigment in the blood, urine and stool, we can then approach the unclassified with a well tried method and learn just what is happen-

ing in the way of bile pigment formation, distribution and elimination. There is no proof in laboratory studies that absorption of bilirubin from the intestine ever occurs in significant amounts, and no clinical experience that suggests such a mechanism. There is good evidence from experiment and from the clinic that bile pigment after being converted to urobilin is reabsorbed—and that such reabsorption serves to accomplish the formation of bilirubin anew. *There is in all likelihood absorption of both bilirubin and urobilin from the gall bladder into the blood or lymphatics.* There is good reason to believe that bile pigment can find its way into the intestine by way of the blood—when ducts are obstructed—but only when there is much in the blood and then sufficient amounts leave the blood to produce small traces in the stool.

There is but one way to increase the total output of bile pigment or to augment the product of the reticulo-endothelial system—and that is by increasing blood destruction. Rous and Brown (17) have shown that after violent exercise there is loss of red blood cells and increase in bile pigment. The well known fact that the stools in pernicious anaemia contain an enormous excess of pigment is another statement of the same condition.

Even though bile pigment output is the result of red blood cell destruction, daily estimates of bile pigment cannot be taken as the index of red blood cell turnover. The methods are not accurate enough and too many variables are uncontrolled. Studies in total bile pigment output are useful in

classifying the anaemias even when no jaundice is present.

From my own studies in the ordinary and well known forms of jaundice I can generalize as follows—that in catarrhal jaundice, in the early stages, there is a period when bile pigment is excluded from the intestine and increases in amount in the urine and in the blood. Coincident with the reappearance of bile pigment in the stool there begins to be a diminished amount in the blood and in the urine. At no time is there any striking increase in the entire output of bile pigment in a way to suggest an over production.

Biliary colic resulting in obstruction of ducts may be followed in eight to twelve hours by icterus of the plasma; further, colic can occur without any demonstrable icterus; that icterus is less likely to result from obstruction of short duration if the gall bladder be normal. When the gall bladder is no longer able to function icterus results in shorter time after obstruction. In Laennec's cirrhosis, I have found that on rare occasions there is diminished amount of bile pigment in the stool coincident with decreasing amounts in the blood and urine. Some patients in this group show relatively little bile pigment formation and for several weeks may have moderate jaundice, with little bile pigment in blood, urine and stool.

Following this period of diminished pigment output, there is a period of increasing jaundice with increased amounts in blood, urine and stool. In lobar pneumonia bile pigment has been found to be increased in the stool at the same time that it is increased in the blood and in the urine. Strange to say, there is no demonstrable anaemia following this apparent over production of bile pigment. In pernicious anaemia bile pigment has been greatly increased in the urine, and in the stool simultaneously, but present only in the urine in the form of urobilin. This great increase is never found in any form of secondary anaemia.

These generalizations are not final—they are subject to revision as more work is done, but we think that as long as jaundice is no better understood we should stick to measurements and not go in for tests. All this discussion can be briefly summarized as follows: Until the pathology of the liver and the reticulo-endothelial system is better understood, jaundice should be regarded only as a symptom and not a disease entity—it should be measured only and not tested for.

Present day views of bilirubin physiology are in all probability correct as announced, but no new methods of study are as yet good enough to displace the old.

# The Differential Diagnosis of Gall Bladder Disease\*

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THE gall bladder must be considered as an integral part of the hepatoenteric system. We must think of the liver as one unit and the intestinal tract as the other unit, the two associated by connecting links which the French call the hepatoenteric circulation. This conception is vitally important, as it emphasizes the complete dependence of one link of the chain on the other portion, the afferent chain connecting the digestive tract to the liver and the biliary tract, the great efferent chain. The liver, like the kidneys, is to a large degree the excretory organ. The biliary tract is the transit system for bile, and the gall bladder is a diverticulum in the course of this transit system. It certainly plays no very active part in upper abdominal digestion. The lack of the organ in many animals and the comparatively unimpaired digestion which occurs in individuals who have been submitted to cholecystectomy bear out this view.

Twenty years ago the diagnosis of gall bladder disease was confined to those cases with biliary colic and sharply circumscribed pain in the upper right quadrant. Today, owing to

modern methods and by a more perfect correlation of surgical and medical material, the refinement of the biliary tract diagnosis has approached that stage where it is possible to assume that many forms of gall bladder disease do not present this classical picture. Before discussing my own experience, I would emphasize these fundamental facts regarding gall bladder disease as I see them.

(1) Gall bladder disease is an effect rather than a cause; a result rather than a provocative agent in many of the cases which we encounter.

(2) It cannot be divorced from the central hepatoenteric system of which it is a link or chain.

(3) The gall bladder may be considered as an actual functioning diverticulum in the afferent transit system from the liver to the bowel.

(4) Gall bladder disease rarely exists alone. There is an abundance of clinical and surgical evidence to prove (1) that the liver is usually implicated. Graham, Judd, Heyd and Kilian and MacNeal, and Tietze have emphasized and proved beyond a doubt that liver disease is a common association of biliary tract disease. Sudler goes so far as to contend that there is lymphatic drainage both ways, from the gall bladder to the liver and

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vice versa. One need only to read the admirable brochure of Heyd and MacNeal to be convinced that cholecystitis is only part of a generalized chronic infection. (2) Cholecystitis is frequently associated with a certain degree of pancreatitis. Of 1,290 cases reported by Judd 347 or 26.8% had associated pancreatic disease; and Piersol and Bockus present evidence to show that in 85% of gall bladder disease there was a reduction in over 50% in the amount of one or all the enzymes. (3) The colon is nearly always affected in some way. This is confirmed by both X-ray and clinical evidence; (4) and in the great majority of instances, the portal system is involved. This means that apart from hematogenous infection with the implantation of specific organisms and the contiguous lymphatic association, the contention of Chauffard is not so far wrong. He points out that the sequence of events in biliary disease and cholelithiasis is (1), the character of the bile will in a sense dominate gall bladder function; (2), the condition of the liver cell will dominate the characteristics of the bile; (3), the condition of the portal blood will dominate the condition of the liver cell; (4), and finally, the status of the digestive tract proper from the stomach to the colon will determine the status of the portal blood. Apart from focal infections and contiguous inflammations this sequence of events with its multitudinous possibilities would seem to dominate the biliary tract.

## II

Gall bladder diagnosis two decades ago consisted in a well taken history

and a careful examination. Today it consists of the same procedure amplified by methods which throw more or less direct light on gall bladder function and pathology. We have at our disposal the following methods:

- (1) History
- (2) Physical examination
- (3) X-ray examination
- (4) Duodenal intubation
- (5) A study of blood serum, notably the Van den Bergh reaction, the icterus index, blood cholesterol and so forth. To these are appended the separate studies necessary to crystalize a diagnosis in any of the adjacent organs.

Let us consider for a moment the history. A history of biliary colic or sharply defined upper right sided pain more or less circumscribed to the biliary region and in the right upper quadrant is encountered in the majority of cases.

Pain in gall bladder diseases, according to Rolleston, is due to two factors: first, acute inflammation of the gall bladder per se, and second, muscular spasm set up by the presence of the calculus in the duct. The pain in cholecystitis varies according to whether or not there is a stone attempting to pass along the cystic duct. When there is a stone, the pain is generally localized to the region of the gall bladder, or if there be contiguous peritonitis, adhesions, or bands (as is not uncommonly the case) the pain may be diffused over the right side, and even to the chest or to the left side. If the liver and gall bladder are much enlarged downward, the pain may extend down to the iliac fossa



and even down to the lower extremities. When there is a stone in the neck of the gall bladder or in the cystic duct, the pain radiates also to the area beneath the inferior angle of the right scapula. This corresponds to the level of distribution of the eighth dorsal segment from which the gall bladder derives its main nerve supply. In uncomplicated cases, pain is not felt in the right acromial or clavicular regions, but in the right hypochondrium or in the epigastrium alone.

That areas of hyperesthesia do occur in acute biliary disease was well borne out by the findings of Livingston, who emphasizes tests for local cutaneous hyperesthesia as part of a routine physical examination for the diagnosis of acute biliary disease. Of his 50 cases, with but two exceptions all tested patients had positive cutaneous hyperesthesia. Of the two negative patients, one had both gall and kidney stones as concomitant findings and positive skin findings for nephrolithiasis was obtained. The other patient did not have acute colic but merely an increasing jaundice due to a stone.

In a review of the literature, we have arrived at the conclusion that pain in gall bladder disease is as variable as the pain in appendicitis. In other words, the pain may vary from an anginal type to one resembling that of a retroversion.

We note, however, that catarrhal cholecystitis gives a different story from pericholecystitis, that stones in the gall bladder, cystic duct, common duct and ampulla evolve differently. I realize in presenting statistics before

this association that they are medical and not surgical and they are open to the serious criticism that pathology may not exist; but right here I maintain that the surgeon demonstrates gross pathology but has no means on the operating table of demonstrating the functional disturbances and incipient pathology which must be present in the large number of cases. He can scarcely believe the findings of Heyd, Tietze and others, who demonstrate histological liver changes when before his own eyes no such change was apparent. According to my own files I have diagnosed some form of gall bladder disease in the last five or six years in over six hundred cases. In going over a consecutive series of 200 cases in which I selected localized circumscribed tenderness over the gall bladder as a subject for analysis, selecting the first 200 cases in which this symptom was clearly presented and accompanied by other signs of biliary disease, in 59% the history was that of typical colic or clean-cut epigastric pain along the right costal margin. In other words, in 59% there was the clinical history concerning which there was very little doubt regarding the diagnosis; in 5.5% the patient complained of burning, showing little or no relationship to the ingestion of food; in 21% the dominating symptoms were those of toxemia with headache, nausea, vomiting and dizziness, and a subsequent survey revealed disease of the gall bladder occurs atypically; in only 5.5% was the evolution of the history such as to suggest the serious problem of an ulcer of the stomach or duodenum;

in 2% of this number there was an absolutely typical migraine; in 3% of the cases the character of the symptomatology was such as to seriously suggest angina; in only 1.5% of cases was there clear left-sided pain which is often explained by a pericholecystitis. In other words, in 41% the symptomatology was atypical and there was evidence to indicate the presence of gall bladder disease. Akana, Greveley and Farr in the study of pain and gall bladder disease note in the great majority of cases pain in the typical site in the right hypochondrium, in 78.4% of cases, with a radiation to the shoulder and back in 28.9%, but the physician sees cases of gall bladder disease in which pain plays no sign. In fact, in our series 10 cases presented were without any sign of pain, but a survey revealed gall bladder disease. In every one of these cases reported there was localized tenderness. In 121 or 40.5% there was diffuse constipation; only 10 or 5% had pronounced looseness of the bowels; 34 or 5% had either the picture of colitis or normal movements; in 45% the appetite was conserved; 24% or so fair; 31%, poor or gone. In nearly all cases after an attack the appetite disappeared for a period. In practically every single case gas usually of the aerophagic type played an important role, in some cases an extremely persistent role. Outspoken jaundice was found in 29—14.5% of this series. The point which I wish to make is to my mind in a certain group of cases gall bladder pathology indicates itself to the clinician with localizing symptoms; with another group it is associ-

ated with toxic disturbances incident to disturbed intestinal or hepatic function of which it is only a part; and finally there is a psychology to the gall bladder case with insomnia, wakefulness usually at 2 o'clock in the morning, and restlessness so that 74 or 37% of the cases which we saw had disturbed sleep or were troubled with insomnia. This association was pointed out by Parturier. The typical history and the atypical history of the type just mentioned, but more particularly the chronic upper abdominal invalids whose symptoms show no direct or synchronous association with the gastric digestive cycle can be viewed as gall bladder suspects. One of the most interesting things to me is the cardiac association, varying all the way from palpitation, tachycardia, mild flutter, arrhythmia to definite angina. Several of these patients were subsequently known to have anginal manifestations. The important point, however, is that angina can be associated with biliary pathology, a very important point to determine. In 71 (35.5%) of all the histories that we went over there was evidence of some cardiac consciousness of the type mentioned. The cardiac association has been pointed out by W. J. Mayo. He also insists upon the widespread effect of biliary disease in producing renal and arthritic symptoms as well.

We then turn to the physical examination. Nothing to my mind is more suggestive than residual tenderness at or near the tip of the ninth costal cartilage and more pronounced on upward pressure. This is enhanced by a fluoroscopic examination by which

it can be definitely demonstrated that tenderness is outside of the duodenal shadow. Unless the attack is recent and the symptom diffuse, tenderness is often fugitive, but residual circumscribed tenderness after an attack is of the most value. A palpable tumor of the gall bladder is, as Mateer and Henderson have pointed out (1), empyema; (2) hydrops, usually associated with stone in the cystic duct; (3) carcinoma; and (4) an occasional gall bladder filled with stones. Rigidity of the upper right rectus, cutaneous hyperesthesia localized to the gall bladder area as Livingston has described are of value. Operation and cholecystography show the variations in gall bladder position, and enhance the value of tenderness outside of the duodenal shadow on fluoroscopy. It is needless to point out that palpation will determine the presence of physical signs over the colon, evidence of the possibility of appendicitis, and the possibility of a right renal lesion as a cause for symptomatology.

I place X-ray examination third because X-ray study usually establishes the anatomic diagnosis, while duodenal intubation like gastric analysis is in a sense a study of impaired physiology. The X-ray study of the gall bladder as carried out today includes three procedures: (1) flat plates; (2) indirect signs; (3) cholecystography. I can recall that 10 years ago I found only 23% of demonstrable gall stones were visualized on the X-ray plate, but by the use of modern technique, better instruments, the Bucky Diaphragm, and double intensifying screens, the percentage of visualized

stones or visualized gall bladders is very much higher. There are naturally differences due to technique which vary in different parts of the country. Furthermore, there are several methods, each of which has its adherents in the performance of this procedure. I still believe that a visualized gall bladder is not a normal gall bladder even though it is not a surgical gall bladder.

To me the indirect signs which are frequently observed in gall bladder disease are of great importance. A host of observers, George, Carman, Holzknecht, Kilian, Belden and others, have pointed out the effect of a gall bladder lesion on the associated gastroduodenal shadow. To me the most important are: (1) tenderness outside the duodenal shadow, upward and to the right. In this series that I studied practically every individual presented this symptom; in fact, I doubted the diagnosis if deep palpation revealed little of importance.

(2) An adhesion deformity, fixing the second portion so that its course follows an abnormal deviation to the right, and gives the impression of being fixed along the lower border of the liver or to the gall bladder region. All varieties of duodenal defects can be encountered from fixation, looping, and marked structural defects.

(3) Adhesion defects with saw-tooth serration of the superior margin of the duodenal cap.

(4) A variation of this is looping between the first and second portion of the duodenum before mentioned, but at operation this finding may be encountered when the duodenum is

attached anteriorly to the gall bladder, and the gall bladder may be normal. I have seen this occur on several occasions.

(5) A pressure defect of the duodenal bulb, smooth, well defined, and indicating according to Belden that the tension in the gall bladder is greater than the normal gastric or duodenal tension, which is the reverse of health. This finding, if present in serial photographs, suggests extraduodenal pathology, usually gall bladder.

(6) Permanent distortion of the duodenal bulb, either through spasm or displacement on its axis is far more common in gall bladder disease than it is in ulcer of the duodenum.

(7) Defects of the second and third portion of the duodenum may mean diffuse inflammation of the upper right quadrant resulting in adhesion formation, partial duodenal stenosis, and even diverticular formation owing to fixation at two different points seen in extensive pericholecystitis and in my own experience even more frequently after the operation of cholecystectomy. Adhesion defects involving the pylorus, pyloric antrum, hepatic flexure or beyond this point produce the so-called pseudohepatic flexure of George and are all significant diagnostic points of pathology in the upper right quadrant, most often pericholecystic in origin. In this series of studies of 200 consecutive cases there was an abnormal, or fixed or unusual arrangement of the duodenum in 49 cases or 24.5%; there was a defective cap in 23 (11.5%); there was marked spasm of the cap in 8.5%; there was distinct looping in

6 or 3%; there was angulation and lateral fixation pronounced in 9 (4.5%); there was distinct diverticular formation in 3 or 1.5%; and there was a typical pressure defect in 6 (3%) of cases, and in a larger number where the defect was by no means so pronounced; in 8, (4%), there was definite fixation of the hepatic flexure of the colon; and in 2 cases there was the pseudohepatic fixation of George.

Regarding the stone shadows which are encountered Rowden, quoted by Moynihan, gives these as follows:

- (1) "opaque and solid"
- (2) "The new moon" or "crescentic type"
- (3) "the wedding ring" shape from later calcium deposits
- (4) "the mosaic" due to overlapping

The third method of X-ray diagnosis consists in the visualization of the gall bladder by means of a dye. This study to my mind is one of the most helpful in the entire category of diagnostic aids. The Graham test as evolved by that distinguished observer is in my judgment without a question one of the great discoveries of this present contemporaneous era of medicine. I can do no better than to refer to the last and most recent communication by this author, which I believe shows without a doubt the present status of this test. It is considered a routine in the complete investigation of any suspected gall bladder case. I am sorry that I cannot contribute to the already large group of statistics. I have already a number

of cases. I inquired just before I left as the number of cases which had been examined in the Jefferson Hospital in Philadelphia. I was informed that since June 15th, 1926, six hundred cholecystograms had been performed. To my surprise only 22 were operated on, all but one out of the 22 having been correct. Before I left Philadelphia I added another to that number, a positive cholecystogram with definite cholecystitis at operation. "Graham in a recent article (*Surg. Gyn. and Obst.*, Feb. 1927, vol. xlv, No. 2, p. 153) discusses the present status of cholecystography. He points out that this method provides a means of investigating the only functions of the gall bladder which are known at present, namely, the ability to concentrate its contents as revealed by an increasing density of the shadow and the ability to store bile as shown by changes in the size of the shadow. It is not only useful in diagnosing cholecystitis, but it has been of importance in recognizing many more cases of calculi than have been possible by the ordinary X-ray examination; by revealing pericholecystitis and pericholecystic adhesions by positively identifying shadows seen on the plain film as being related to the gall bladder or not; and of showing the various anomalies and abnormalities such as diverticula, double gall bladder, and so forth. He points out that in his own experience a total of 1246 patients were examined by this method. The gall bladder was removed and submitted to microscopical examination in 147 cases. In 143 of these 147 cases the X-ray diag-

nosis was confirmed, showing a percentage of correctness of 97.28%. He gives a table recording the cases reported in which the cholecystographic examination has been confirmed with operative findings. The oral and intravenous methods are also mentioned. This table shows a percentage of correctness in 446 cases of all authors in the diagnosis of pathological gall bladders to be 97.8%; the percentage of correctness in 115 cases of all authors with a diagnosis of normal gall bladder equals 74; the percentage of correctness in 380 cases by all authors by the intravenous method is 95%; a percentage of correctness in 181 patients of all authors by the oral method equals 89%. Graham points out that he still feels that the gall bladder empties itself of its contents through the cystic duct by washing out its contents by bile from the liver, by the elasticity of the contractile mechanism of its walls, and by variations in intra-abdominal pressure."

More difficult to interpret are the poor shadows and delayed evacuation. I am convinced that a positive cholecystogram can be converted into a negative cholecystogram by medical therapy. I am also convinced that there are variations in response dependent entirely upon non-surgical functional alterations in the organ. I am also convinced that the Boyden meal will induce a greater reduction in the shadow than duodenal intubation and stimulation.

Duodenal intubation is now a standard method of biliary tract investigation. Thanks to my colleague, Dr.

Lyon, it is possible to segregate the bile which is obtained by this method in such fashion that a reasonable clinical interpretation can be attached to the finding. Even before this method was routinely used I studied the duodenal secretion for evidence of biliary mal-function, but I feel that it is important to attempt segregation of specimens in the hope of obtaining definite results. My objection to some of the critics of this method is that they fail to carry out the test in the proper way. It is frequently impossible to obtain on a single examination sufficient stimulation on the first application. I have repeatedly seen four to five tests of the duodenum reveal pathology in only one or two of the aspirates. Furthermore, those who carry out this technique must be familiar with the characteristics of the duodenal contents in health. I believe this is one of the most important things most men fail to do. They must also be informed as to the rationale of the sequence of bile after stimulation. It is likewise essential for the hospital internist or the technician to study normal duodenal contents before the pathological are encountered. While I do not agree with Lyon in all his contentions, I agree with the fundamental principles. I personally feel the necessity of the careful correlation of all data, and to me the microscopy of the bile is the most important, the color sequence of relative importance, and the bacteriology unless associated with pure cultures and plain evidence of infection, the least important. The latter is evident from a more recent study by

Judd, Mentzer and Parkell. There is a frequent discrepancy between duodenal cultures and cultures from the bile in the gall bladder. What makes gastric and duodenal cytology so difficult is the more or less constant swallowing of oral secretion. Jackson believes that the principal function of the esophagus next to food transit is the swallowing of saliva, many ounces of which are daily assimilated in this way. I believe:—

(1) That leucocytes increased, clumped and stained are practically always evidence of inflammation or infection, depending upon the particular increment involved, they may suggest trouble in that segment.

(2) The presence of characteristic rows or layers of fan-shaped rosy collecting or columnar bile duct epithelia if pigmented, and when associated with the above are extremely suggestive of angiocholitis or even cholecystitis. They differ from duodenal epithelia in that the latter are cuboidal or ovoidal in type.

(3) Crystals, more particularly cholesterol crystals and the so-called calcium bilirubin type, but particularly the former are evidence of biliary stagnation and I believe evidence of potential gall stone formation. In two cases I had operated on in which no stones were found, this finding was constant, one of black, tarry bile with a puree of cholesterol crystals was found. Lyon believes that in cystic duct obstruction no B fraction is obtained and it is accompanied by the discharge of characteristic flocculi of yellowish brown mucus in shaggy, slimy amounts, often twisted by the

rifling of the cystic duct and encrusted with bile salts; and finally, the presence of bright yellow oleaginous material which melts out into globules, pools or lakes, particularly if the slide be heated; and a lack of normal B bile may mean cholecystitis, adhesions, stone impaction, stricture, and angulation of the ducts.

Finally, I believe that the amorphous material obtained by ordinary drainage, and not produced by the spurt of acid gastric juice, is very significant. Recent studies of our own suggest that there is a high melting-point fat in this amorphous material, and it may be significant as the crystals mentioned above, as an indication of potential stone formation.

Duodenal intubation to me is a physiological study of the biliary tract together with an attempt to demonstrate pathology by cytologic means. I can realize its dangers, but I feel it simply adds one more link in the chain of evidence. I believe that chronic biliary disease was usually associated with a disturbance in the gastric secretory output of the downward type. In this group 37% showed a total acidity over 60 after an Ewald test meal; 21% showed an acidity between 40-60; 42% below 40. It is therefore apparent that a reasonable high percentage have not only an intact secretion but an exaggerated secretion. The interpretation of this finding will of course be dependent upon the associated pathology.

Time does not permit me to mention the value of the study of blood in gall bladder disease, but most clinicians are today interested in the quantitative de-

termination of serum bilirubin in demonstrating latent jaundice as revealed by the Van den Bergh serum reaction and the icterus index. I believe that obstructive jaundice in order of its evolution is exactly as Heyd has mentioned:

- (1) gall stones
- (2) angiocholitis or catarrhal jaundice
- (3) cancer of the liver
- (4) cirrhosis
- (5) cancer of the ducts and gall bladder
- (6) cancer of the pancreas
- (7) gastric and duodenal cancer

The presence of colicky jaundice with acute biliary obstruction and acholic stools is too well known, but as Haggert points out the characteristic diagnostic symptoms of common duct impaction by stone are:

- (1) colic
- (2) sepsis
- (3) intermittency
- (4) chronicity, and to which I would add
- (5) a negative cholecystogram
- (6) a direct Van den Bergh reaction
- (7) acholic stools

and the general urinary and skin manifestations. In the majority of common duct obstructions by calculus, as Courvoisier points out, the gall bladder is atrophied. It is interesting to mention in this connection the study of the circulating blood for cholesterol was tried out by us some years ago in the hope that hypercholesterolemia might offer an efficient differential diagnostic aid in gall stone cases. We had a series in which the cholesterol

content was distinctly increased, but I can recall the first operative case where this finding was not present. The patient had only 166 mgm. Shortly after that another case came to operation with the same finding, and we gave up that method of investigation. To my mind today the situation is very much clarified. It is my belief that at some stage in the evolution of the cholesterol stone there had been an increased blood cholesterol. We now know that an increased cholesterol content can occur for periods of time followed by a distinct diminution. A study of blood cholesterol, therefore, simply indicates the existing content at the time of testing.

In the differentiation of other conditions from gall bladder disease I would name the following as the most important:

Gastric disease is differentiated (1) in the history by the fact that the gastric symptoms usually occur at a definite period in the gastric digestive cycle. (2) The physical signs are rarely localized over the gall bladder unless there is associated pathology. (3) The gastric analysis of duodenal ulcer, from which the differential diagnosis must so frequently be made, shows a different sequence, and in my experience 78% of duodenal ulcers give a characteristically high climbing curve and 96% give a characteristic defect on X-ray examination. Finally, if the X-Ray study of the stomach is negative and also the gastric analysis, flatulent indigestion, symptoms showing no relationship to the gastric digestive cycle, distress and discomfort persisting in spite of gastric therapy, night

pain rather than day pain, are all suggestive of biliary rather than gastric pathology. In the differentiation of duodenal ulcer and duodenal diseases, most of these conditions show a certain sequence to gastric digestion. This is particularly seen in the characteristic sequence of duodenal ulcer. Most important are the gastric findings already mentioned. Unless there is periduodenitis the cap is usually movable and the defect is more or less characteristic. The history, gastric analysis, and the X-ray findings will usually enable one to make the differentiation.

Regarding pancreatic diseases, my own experience tells me that this diagnosis is most frequently made by an examination of the movement and by the pressure defects which occur on the X-ray study. In my experience, pancreatic disease most frequently produces a rather characteristic failure of assimilation of fats, and not infrequently of proteins and carbohydrates in the stool. It also produces a pressure defect, flattening out the duodenum when the head of the organ is involved, or producing a pressure defect on the stomach. The value of duodenal intubation and a study of the duodenal ferments to my mind has not yet reached that stage where it is possible to make an early diagnosis. We spent two years studying the ferment activity of the duodenal contents, and I regret to say that our conclusions except in rather advanced disease were not satisfactory. However, this is of value and might be combined with fecal studies.

The study of the liver includes not



only the history, the physical examination, the X-ray determination, but a series of functional tests, most of which throw some light on one of the various functions of the liver. A large number of tests have been devised, but most clinicians are content to study the blood chemistry, determination of segregation of dye with tetrachlorophthalin, the study of C bile or liver bile, and the feces, and if necessary perform the ordinary carbohydrate tolerance tests. Many other tests have been devised but unfortunately do not throw light on the total function of the liver.

Among other differential diagnoses which must be made are those which separate angina, renal stone, enterospasm, chronic appendicitis as well as lead colic. As I have already mentioned, cardiac manifestations are very common in gall bladder disease, amounting not infrequently to actually a form of pseudo-angina associated with marked aerophagia, probably a vagus phenomenon. On the other hand, I have seen angina associated with gall bladder disease, and I feel in every case of angina one should carry out the routine tests such as duodenal intubation and cholecystography to determine the efficiency of this organ. The tendency of angina to become aggravated on effort, the evidence of vessel sclerosis, myocarditis, and the studies of the cardiologist will make this differentiation. In some cases it can almost be mimicked by gall bladder disease. Tabetic crises call for a careful examination in every instance of the reflexes, pupils, blood chemistry, and if necessary examination of the

spinal fluid. These attacks can be fulminating and I have seen them mimick almost exactly a severe attack of biliary colic. Renal stone may produce severe pylorospasm, hypersecretion, nausea and vomiting, and resemble biliary colic. A study of the urine, the associated urinary phenomena, the fact that the symptoms predominate posteriorly rather than anteriorly, although this is not always the case, and a plate of the renal region will usually clear up the diagnosis. Patients have been operated on for enterospasm, which in my experience is a very common association of gall bladder disease. In 34 of these cases there was very pronounced enterospasm amounting in some cases to a spastic bowel obstruction. In the great majority of cases of gall bladder disease at some time or other there is associated spasticity of the left side of the bowel; constipation is usually spastic in type. In a careful survey using the above methods, however, the spasm will be evident, and where there was a reasonable doubt and the cholecystogram is negative, particularly in that small group of cases where there is lower left-sided pain, a colon injection will usually clear up the picture. Appendicitis, particularly when retrocecal and pointing upward, can give rise to a great deal of trouble. The roentgenological study of this region, particularly the late plates after the cecum has emptied, will often be helpful. The nature of the attacks, the localization of tenderness, the demonstration of normal findings in the gall bladder region, will usually make the differentiation. However, one must realize

that chronic appendiceal and gall bladder disease are very frequently associated. Lead colic is mentioned as a cause. However, the condition of the red cells and the blue line on the gums, the history of the ingestion of lead, and the general spasticity of the colon, will usually make the differentiation.

It is my belief that wherever gall bladder disease is suspected it is wise to carry the patient through the entire group of procedures, beginning with duodenal intubation, following through with a complete X-ray study and finally the blood serum and even the

movement. I feel satisfied that a careful study of this type including these various procedures will in most instances enable the observer to make a correct diagnosis. As internists we must realize, however, that gall bladder disease is frequently associated with colon disease, chronic appendiceal disease, chronic liver disease, pancreatic disease, heart disease, arthritis, and severe secondary anemias. It is therefore apparent that in this large group of clinical conditions a survey of the gall bladder is an important part of the complete study.

# Roentgenographical Aspects of the Differential Diagnosis of Disease of the Gall Bladder\*

By B. H. NICHOLS, M.D., *Cleveland Clinic, Cleveland, Ohio*

THERE is no more fertile field for the roentgenological study of pathological conditions than that presented by the upper right abdominal quadrant. It is the uncertainty which attends the diagnosis of lesions within this area that has for so long demanded the exploratory operation. This is well illustrated by the finding in a recent survey of the cases of hydronephrosis of the right kidney seen at the Cleveland Clinic that in thirty per cent of these cases an exploratory operation had previously been performed for a supposed gall-bladder lesion or other abdominal disorder. The time has now arrived, however, when every patient with clinical symptoms referable to the right upper abdominal quadrant has a right to demand an accurate diagnosis, this assurance being largely due to recent developments in the field of roentgenology, principal among which are duplitized films, the Bucky diaphragm, and the use of opaque substances for the study of the abdominal viscera. Today, by a systematic roentgenographical study in the light of the clinical history presented in each individual case, the differential diagnosis can usually be established.

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In the investigation of the right upper abdominal quadrant our usual procedure is first to take a film of the kidneys and lumbar spine. This enables us to exclude or to determine the presence of a pathological condition of the spine, such as Pott's disease, malignancy, or hypertrophic arthritis, the last of which in particular, often causes pain in the right side simulating that due to a kidney stone or to a diseased gall bladder. The next step is to place the patient in the prone position and to take a series of gall bladder films with varying degrees of exposure. In the event of a suspicious shadow, a comparison of these films with the kidney films enables us to determine whether the calculus is anterior and hence probably a gall stone, or posterior and probably a kidney stone. The gall bladder films may disclose a long, palpable lobe of the liver, thus establishing the identity of a palpable tumor in the right upper quadrant.

From the survey of the first films we may determine the presence of an atrophic kidney, a large kidney, an irregular kidney, a polycystic kidney, a tuberculous kidney, a tumor of the kidney, a large hydronephrosis, or a ptosed right kidney. Further to confirm the diagnosis, catheterization of the ureters with X-ray catheters fol-

lowed by an X-ray examination will establish the cause of an ureteral obstruction, in case the catheter fails to pass up to the kidney pelvis, or it may disclose the presence of a double ureter. Suspicious shadows in the right side may appear to be in contact with the X-ray catheter. In such a case X-ray films should be taken with the patient in two positions in order to determine whether these shadows are from calcified glands or from some other source outside the ureter. These shadows may not appear to be in contact with the catheter in either position, or they may appear in contact in only one position. However, since occasionally shadows which appear to be at some distance from the catheter in both positions may nevertheless be stones in a redundant ureter or in a large dilated ureter, this examination should be followed by the injection of an opaque medium into the ureter and kidney pelvis to determine the size, shape and position of each. By this means an obstruction or a narrowing of the ureter from an ureteral calculus or a stricture may be seen; a bifurcation of the ureter may also be determined by this method.

After these two sets of films have been taken, the stomach is filled with a barium meal and observed fluoroscopically and by films to determine the presence of an ulcer or tumor, and also to discover the position and mobility of the stomach. As the barium passes into the duodenum, that also is examined to determine (1) its position; (2) the presence of an ulcer or of adhesions; and (3) the possibility of duodenal stasis, as disclosed by dilatation and retention. We have

found that this last condition is often the cause of periodical headaches with vomiting of bile, and also of epigastric pain. Many patients who are suffering from duodenal stasis have undergone operations for suspected gall bladder disease without securing any relief from their symptoms. We now consider that a dilated duodenum is a distinct clinical entity; and we have found that in many instances relief from symptoms is secured by operation. This condition, therefore, should always be ruled out in cases of bilious headache, especially when there is a history of their occurrence over a period of several years.

Six hours after the examination of the duodenum another fluoroscopic examination is made and films are taken to determine whether or not there is any gastric retention. This examination may be of much importance in cases of carcinoma or of ulcer in particular, in indicating whether or not an operation should be performed. Even in advanced cases of carcinoma with retention a gastro-enterostomy should be done if sufficient stomach-wall is free from infiltration. Whether or not this is the case can usually be determined by the X-ray examination.

This opaque meal is followed through the intestinal tract and a barium enema is given on the following day to determine whether or not any pathological condition is present in the colon. Often this study discloses an abnormality in the position of the duodenum or colon in the right upper quadrant, thus indicating the presence of an extensive lesion which it is possible to identify as a carcinoma of the head of the pancreas.

Should the above consecutive examinations not indicate any pathological condition which accounts for the symptoms, then a gall bladder dye may be administered according to the plan outlined by Graham of St. Louis. This consists in giving the patient five capsules of one gram each of tetraiodo-phenolphthalein with the evening meal, each capsule being incorporated in a large capsule of soda. Gall bladder films are taken at 9 A. M., 1 P. M., and at 2 P. M. on the following day, after a meal rich in fats. If the gall bladder is normal it will be filled at 9 A. M., the shadow will be dense at 1 P. M., and the gall bladder will be almost empty at 2 P. M. on the following day. If it is not empty then, another X-ray film should be taken on the following morning. If no dye is seen in the gall bladder and the capsules have broken up in the intestinal tract, a diagnosis of gall bladder disease may be made. By this examination it is possible to determine whether or not the gall bladder is receiving bile, and if so how rapidly; and its emptying time can be determined. The dye also establishes the position of the gall bladder and may thus rule out an erroneous interpretation of a suspicious shadow which does not lie in this area. Moreover, a large stone in the gall bladder may show through the dye in the gall bladder as a shadow of definitely lesser density; and finally, the shape and location of the gall bladder may show whether or not there are adhesions to the duodenum.

Our findings in 418 cholecystograms may be summarized as follows:—

A pathological condition indicated in .....240  
No pathological condition indicated in.....171  
Doubtful ..... 7  
Number of cases in which cholecystograms were followed by operation—26.

Comparison of cholecystographic and operative findings:—

(1) Cases in which cholecystograms showed no lesions but lesions were found at operation—3.

Stones ..... 2  
Cholecystitis ..... 1

(2) Cases in which the indication of a pathological condition on the cholecystogram was confirmed at operation—21.

Stones .....12  
Chronic cholecystitis..... 4  
Adenocarcinoma ..... 2  
Mucocoele ..... 2

No pathological report 2, but in these cases the gross findings at operation were: in one a fibrotic whitish gall bladder; and in the other a grayish gall bladder showing a moderate degree of inflammation.

(3) Cases in which the cholecystogram indicated the presence of a lesion but none was found at operation—2.

In these two cases the findings were as follows:—In one a soft, normal gall bladder, slightly fibrous wall; and in the other the colon was adherent to the edge of the liver, and the pathological report on the gall bladder was 'cholesterolosis'.

As shown above, in this series of 26 cholecystograms the findings were definitely confirmed at operation in all but 5 cases, or in 81 per cent.

*Case 1-(116,015).* The patient was a married woman, 23 years of age, who came to the Clinic because for two years she had had persistent pain in the right upper abdominal quadrant. This had been diagnosed as due to cholecystitis with stones, and three weeks before she came to the Clinic a cholecystotomy had been performed at which no stones or other pathological condition of the gall bladder had been found. The symptoms had been unrelieved.

An X-ray taken after the injection of sodium iodid showed dilatation of the right ureter above the stricture; and the diagnosis of hydronephrosis was made. Dilatation of the ureter relieved the symptoms.

In this case if a complete roentgenographical study of the right kidney and ureter as well as of the gall bladder region had been made when the patient first consulted a physician, she would have been spared an unnecessary operation.

*Case 2-(114,047).* The patient was a married woman, 38 years of age, who came to the Clinic because of persistent pain in the right side. This

pain was characterized by severe spasms passing to the back and was associated with nausea and vomiting. She had had attacks of this kind during a period of about four years, the character of the pain and its intermittent nature giving rise to the suspicion that she had gall-stones, although there had been no jaundice or change in the color of the stools. On palpation of the right upper quadrant a tumor-mass was evident which was tender to pressure, and suggested an enlarged dilated gall bladder filled with stones.

An X-ray examination gave evidence of marked hydronephrosis of the right kidney; gall bladder plates, on the other hand, gave no evidence of any pathological condition.

The pyelogram confirmed the primary finding of hydronephrosis and a nephrectomy was performed at which the diagnosis was confirmed.

Such cases as these illustrate well some of the pitfalls which the physician and the roentgenologist alike must avoid in all cases in which the symptoms are referable to the right upper abdominal quadrant.

# Effects of Sodium Tetraiodophenolphthalein On Some Vital Organs\*

By C. K. HSIEH, M.D., *Peking, China*

THE remarkable Graham method for visualization of gall bladder since its discovery in 1923 (1) is now widely used as a routine procedure in the Roentgen diagnosis of gall bladder conditions. The high toxicity of the tetrahalogenophenolphthaleins employed in this test is well known as evidenced by the reports of some marked constitutional reactions after the administration of the drug sometimes observed in the earlier days of the development of this method of diagnosis. With the improvement of technique of administration and of purer preparation of the salts, however, any untoward effect has been eliminated. The substitution for the tetrabromphenolphthalein with the iodide which is about twice as heavy but has about the same toxicity, thus reducing the dosage to about one-half that of the brom-compound, further minimizes the unpleasant reactions (2). From the clinical standpoint, therefore, it seems this Roentgen visualization test with the sodium tetraiodophenolphthalein has been put on safe ground.

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However, pathological studies of the effects of these compounds have not been extensively done. The originator of the test, Graham, and his associates working with the usual diagnostic dosage of both the brom- and the iodo-salts report that no pathological changes are found in the liver from both the dog and the human. (3) Ottenberg and Abramson (4) in determining the upper limits of the intravenous dosages of the tetrachlor- and tetrabrom-phenolphthaleins find extensive degeneration and necrosis of the liver of animals given doses of from 0.3 to 0.4 gm per kilo of body weight. Doses of from 0.4 to 0.5 gm per kilo kill rabbits at once and the livers are profoundly congested and microscopically there is acute degeneration of the liver cells. In his animals given doses from 0.1 to 0.2 gm per kilo there are no pathological changes in the liver or they are so little as to be considered negligible. These workers are of opinion that there is no gradation between the toxic and non-toxic doses. In the Pathological Laboratory of the University of Michigan Professor Warthin has found some fatty changes in some livers from human individuals after the use of the dye in the Graham test. It is the object of this study to determine whether

these fatty changes are of any significance or not, and also to observe its relationship to other pathological changes such as degeneration and necrosis.

#### PROCEDURE

In this experiment both the intravenous injection and the oral administration of the sodium tetraiodophenolphthalein were used. Thirty-four dogs were divided into two main groups: to one the intravenous injection was given and with the other the dye was administered by mouth. Each of the two groups was subdivided into two: one to determine the effects with increasing intervals of time and the other to observe the effects with increasing dosage. Livers from two cholecystectomized dogs of the surgical department of the University Hospital which were given the dye intravenously to study the bile passages were included in this series. Three normal dogs were used for control.

In Group I the dogs were given doses of 8 grains per 10 pounds in enteric-coated capsules by mouth (approximately 0.12 gm per kilo); and in Group III similar doses were used intravenously. These dogs were killed from within one day to two months. Doses ranging from 3.3 grains (human dose—5 gr per 15 lbs) to 40.0 grains per 10 pounds (about 0.05 to 0.58 gm per kilo) were given to animals of Group II by mouth and of Group IV intravenously; they were killed within one or two days if they survived.

All dogs given the dye orally were roentgenographed or fluoroscoped to note if any of the ingested capsules

were undissolved. Some of those with the intravenous injections were also x-rayed for gall-bladder shadows. The animal dose (8 gr. per 10 lb) in most instances gave good shadows of the gall bladder.

In the intravenous injections 10 per cent solution of the dye was used and the injections were made in the femoral veins with the dogs under ether anesthesia. All dogs were killed with ether. These latter facts are of significance because the little histological changes found in cases given the small doses and in the controls can possibly be explained as the result of ether.

#### RESULTS

*Controls:* Findings of these normal dogs without the use of the dye are taken for control and the fat contents of the organs examined is considered as the standard.

NO.	LIVER	HEART
C-1 1660 LAD	Congestion + Fats + in liver cells and bile ducts	—
C-2 3355 LAD	Congestion + Fats + in liver cells Bile ducts—negative	—
C-3 3347 LAD	—	No fats

*Group I (Table I):* Sodium tetraiodophenolphthalein in enteric-coated capsules was given by mouth in doses of 8 grains per 10 pounds. These dogs were kept from one day to two months. In the liver congestion of various degrees was found in those killed within one week. Slight amount of fat was present in the liver cells of



dogs killed within two weeks and in the bile ducts a small amount of fat was noted in all cases. The spleen showed little changes except congestion. Slight fatty changes were also present in the kidney in all except from 3.3 to 16.0 grains per 10 pounds by mouth there was some congestion but with no fatty changes in the liver. When the dose was raised to two or three times of the animal dose (i.e. 8 gr per 10 lb) in addition to the very

TABLE I

NO.	WT.	DOSE	X-RAY BEFORE OR AFTER DEATH	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS		
					LIVER	SPLEEN	KIDNEY
O-1 1164 LAD	48 lbs.	40 gr.	1 cap undis solved	17 hrs.	Congestion +++ (no fat stain)	Negative	Negative
O-2 1163 LAD	27 lbs.	20 gr.	None seen	17 hrs.	Congestion ++ (no fat stain)	Negative	Negative
O-11 1302 LAD	18 lbs.	15 gr.	None seen	18 hrs.	Congestion ++ Fats + Bile ducts—fats +	—	Congestion ++ Fats +
O-4 1339 LAD	40 lbs.	30 gr.	None seen	1 wk.	Congestion ++ (no fat stain)	Negative	Negative
O-5 1442 LAD	30 lbs.	25 gr.	None seen	2 wk.	Fats + in liver cells and	Negative	Fats +
O-6 1654 LAD	25 lbs.	20 gr.	None seen	1 mo.	bile ducts No fats Bile ducts—fats +	Negative	Fats +
O-7 2088 LAD	15 lbs.	10 gr.	None seen	2 mo.	Negative Bile ducts—fats +	Negative	Negative

*Group 1*—Dogs given sodium tetraiodophenolphthalein in capsules of 5 grains each in doses of 8 grains per 10 pounds by mouth and killed at intervals of from within one day to two months.

in the one killed at two months' interval. Congestion was the only prominent feature in the findings of this group; the slight amount of fat present in the liver cells and bile ducts seems to be compatible with the amount found in the control dogs.

*Group 2 (Table 2)*: With doses of

marked congestion there were considerable changes in the liver cells, disintegration of cells around the central veins (early necrosis) and very marked fatty degenerative infiltration both in the liver cells and the epithelium of the bile ducts. The spleen showed hemorrhages in some cases

TABLE II

NO.	WT.	DOSE	SYMPTOM	X-RAY BEFORE OR AFTER	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS			
						LIVER	SPLEEN	KIDNEY	HEART
O-8 1300 LAD	30 lbs.	10 gr. (man dose)	None	None seen	18 hrs.	Congestion + No fats	Negative	Negative	—
O-11 1302 LAD	18 lbs.	15 gr.	None	None seen	18 hrs.	Congestion ++ Fats + Bile ducts—fats +	—	Conges- tion ++ Fats +	—
O-9 1388 LAD	9 lbs.	15 gr.	None	None seen	24 hrs.	Congestion ++ No fats	Conges- tion ++	Fats ++	—
O-10 1390 LAD	16 lbs.	40 gr.	Very weak	None seen	24 hrs.	Congestion ++++ Early disintegration of central lobules	—	Conges- tion +++	—
						Fats +++ Bile ducts— fats+++			
O-13 1657 LAD	16 lbs.	40 gr.	Very weak	None seen	42 hrs.	Congestion ++++ Fats ++++ in liver cells; ++ in bile ducts. Slight degeneration of cells	—	Conges- tion +++ Fats ++	—
O-14 1658 LAD	16½ lbs.	55 gr.	Very weak and drowsy	3 caps undis- solved	42 hrs.	Congestion ++++ Normal architee- ture Fats +++ in liver cells and bile ducts	Conges- tion +++ Slight de- generation	Conges- tion +++ Fats ++	—
O-15 3548 LAD	15 lbs.	50 gr.	Very weak and drowsy	None seen	24 hrs.	Congestion ++++ Fats ++++ in liver cells and bile duct Marked degenera- tion (early necrosis)	Conges- tion +++ Slight de- generation	Conges- tion +++ No fats	Fatty degen- eration ++
O-16 3549 LAD	13½ lbs.	45 gr.	Very weak and sick	None seen	24 hrs.	Congestion ++++ Fats ++++ in liver cells and bile ducts Early necrosis	Conges- tion +++ Slight de- generation	Conges- tion ++ Fats +	Fatty change ++++
O-17 3550 LAD	16 lbs.	40 gr.	Very weak and sick	None seen	24 hrs.	Congestion ++++ Slight disintegra- tion of cells Fats ++++ in liver cells and bile ducts	Conges- tion ++ Slight de- generation	Conges- tion +++ Degenera- tion of tubules Fats++++	Fatty change ++++
O-18 3551 LAD	10 lbs.	40 gr.	Very weak and sick	None seen	24 hrs.	Congestion ++++ Early disintegration of cells Fats ++++ in liver cells and bile ducts	Conges- tion ++	Conges- tion +++ Slight de- generation Fats++++	Fatty change +

Group 2—Dogs given sodium tetraiodophenolphthalein in capsules of 5 grains each by mouth in doses from 5 grains to 40 grains per 10 pounds.

and degeneration of the cells, particularly those in the pulp. The kidney showed moderate congestion and fatty changes. The hearts of those dogs given the large doses presented degeneration of the myocardial cells with

chloroform poisoning or poisoning with other toxic agents.

*Group 3 (Table 3):* Intravenous injections of the dye in doses of 8 grains per 10 pounds were given to the

TABLE III

NO.	WT.	DOSE	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS		
				LIVER	SPLEEN	KIDNEY
I-1 1160 LAD	65 lbs.	50 gr.	16½ hrs.	Congestion ++++ (no fat stain)	Congestion ++	Congestion ++
I-2 1196 LAD	23 lbs.	17 gr.	16 hrs.	Congestion ++ No fats	Negative	Congestion ++ Fats +
I-3 1338 LAD	25 lbs.	20 gr.	3 days	Congestion ++ (no fat stain)	Congestion +	Congestion +
I-4 1387 LAD	20 lbs.	16 gr.	1 wk.	Congestion ++++ No fats	Negative	Fats ++
I-5 1443 LAD	25 lbs.	20 gr.	2 wk.	Congestion + No fats	Negative	Congestion ++ No fats ++
I-6 1655 LAD	10 lbs.	8 gr.	1 mo.	Congestion ++++ Fats + in liver cells and bile ducts	Congestion ++	Congestion ++ Fats ++
I-7 2089 LAD	45 lbs.	36 gr.	2 mo.	Negative	Negative	Chronic glomerulo- nephritis (apparent- ly not related to action of the dye)

*Group 3*—Dogs given sodium tetraiodophenolphthalein in doses of 8 grains per 10 pounds intravenously and killed at intervals of from within one day to two months.

fatty degenerative infiltration. None of the dogs, however, succumbed, though they were all very weak and drowsy. The findings of this group, namely fatty degenerative infiltration and disintegration of cells of the liver, kidney, and heart suggest a similarity to those generally found in cases of

animals of this group. There was congestion of different degrees noted in the liver, but no fatty changes, except in one dog which had been kept for one month. The kidney showed some amount of fat but this was not constant. The spleen showed practically no changes. The findings, on

TABLE IV

NO.	WT.	DOSE	SYMPTOM	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS			
					LIVER	SPLEEN	KIDNEY	HEART
I-8 1301 LAD	12	4 (man dose)	None	24 hrs.— killed	Congestion + Fats + in liver cells and none in bile ducts	Negative	Congestion + Fats ++	—
I-2 1196 LAD	23	17	None	16 hrs.— killed	Congestion ++ No fats	Negative	Congestion ++ Fats +	—
I-9 1389 LAD	35	56	Vomited Weak and sick	23 hrs.— killed	Congestion ++ Cells—Normal Fats ++ in cells and bile ducts	Congestion ++ Slight degeneration	Negative No fats	—
I-10 1391 LAD	38	92	Vomited Sick and weak Restless Rapid resp.	10 hrs.— died	Congestion ++++ Fats ++++ in cells and ++ in bile ducts Necrosis—central	Congestion +++ Slight degeneration	Congestion ++ Fats +++ Tubular cell cloudy	—
I-13 3230 LAD	19	46	Vomited Very weak Rapid and shallow resp.	4 hrs.— died	Congestion ++++ Early disintegration Fats ++ in cells and ++++ in bile ducts	Congestion ++++ Hemorrhage	Congestion ++ Slight degenera- tion of tubules Fats ++++	—
I-14 3365 LAD	11	26	Very weak and drowsy	7 hrs.— killed	Congestion ++ Early necrosis Fats +++ in cells and bile ducts	Congestion ++	Congestion ++ Cells—cloudy No fats	Degeneration of cells No fats
I-15 3353 LAD	18	43	Very weak and sick Rapid and shallow resp.	8 hrs.— died	Congestion ++++ Early necrosis Fats ++++ in cells and bile ducts	Congestion ++++ Degeneration Hemorrhage	Congestion +++ Desquamation of tubular cells Fats+	Degeneration of cells Fats++++

Group 4—Dogs given sodium tetraiodophenolphthalein in doses of 5 grains to 24 grains per 10 pounds intravenously.

the whole, are similar to those in Group I.

Group 4 (Table 4): With increasing doses of the dye injected intravenously the changes were more evident and extensive than in cases of Group 2 in which the dye was used orally. Three of the four dogs given three times of the usual animal dose

In the kidney, congestion, moderate fatty changes and cloudy swelling, with even desquamation of the cells of the tubules were noted in cases given the high dosage. The spleen showed considerable congestion and even hemorrhages in some cases and degeneration of cells. The heart in two dogs examined showed marked degeneration in both, and marked fatty

TABLE V

NO.	WT. IN LBS.	DOSE IN GRS.	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS OF LIVER
I-11 1656 LAD	32	25	8 hrs.	Congestion ++ Fats ++ in liver and bile ducts
I-12 1788 LAD	35	28	8 hrs.	Congestion ++ Fats ++ in liver cells and bile ducts

Group 5—Dogs cholecystectomized six months previous to intravenous injections of sodium tetraiodophenolphthalein in doses of 8 grains per 10 pounds.

died in four to ten hours after the injection and the fourth one was killed seven hours after the injection. Disintegration of cells of the liver around the efferent veins with very marked congestion was noted in three. Extensive central necrosis of the liver was observed in the other that died in ten hours. This longer period of interval between the injection and death had probably provided sufficient time for the destructive process to go on to actual necrosis while in the other three cases the changes were not completed. Marked fatty degenerative infiltration was found in all these cases and seemed to precede the necrotic changes.

degeneration in the one that died. The cause of death of these dogs was apparently myocardial weakness and failure.

Group 5 (Table 5): These two dogs had been cholecystectomized about six months before the intravenous injections of tetraiodophenolphthalein; the dose was the usual one for dogs as used in Groups I and III. The pathological findings were essentially the same as in those in Groups I and III. The absence of the gall bladder had in no way increased or decreased the effect of the dye on the liver.

## SUMMARY

1. The effects of sodium tetraiodophenolphthalein on some vital organs were studied as regard changes in time and in increasing dosage. Thirty-one dogs were given the dye either orally or intravenously and three dogs were taken as controls.

2. Either orally or intravenously small doses of from 3.3 to 16.0 grains per 10 pounds gave only congestion with but little fatty changes in some cases and these changes were so minimal that they could be considered to be within normal limits. Therefore it is safe to conclude that the ordinary human dose of sodium tetraiodophenolphthalein as used in the Graham test is under the toxic limit.

3. With the larger doses marked degenerative changes were observed

in the liver, spleen, kidney, and heart; fatty degenerative infiltration was the most conspicuous finding in all cases and this seemed to be the forerunning change of actual necrosis. Extensive necrosis was present in one case. In view of these very marked toxic effects with over dosage, therefore, great caution should be taken in the administration of this iodo- or similar compounds.

4. With small doses both oral and intravenous methods of administration of the dye are safe and their effects on the body tissues are apparently about the same in degree. But with over doses intravenous injection of the dye produces much more extensive damage and in shorter time. So in using the intravenous method still greater care should be taken.

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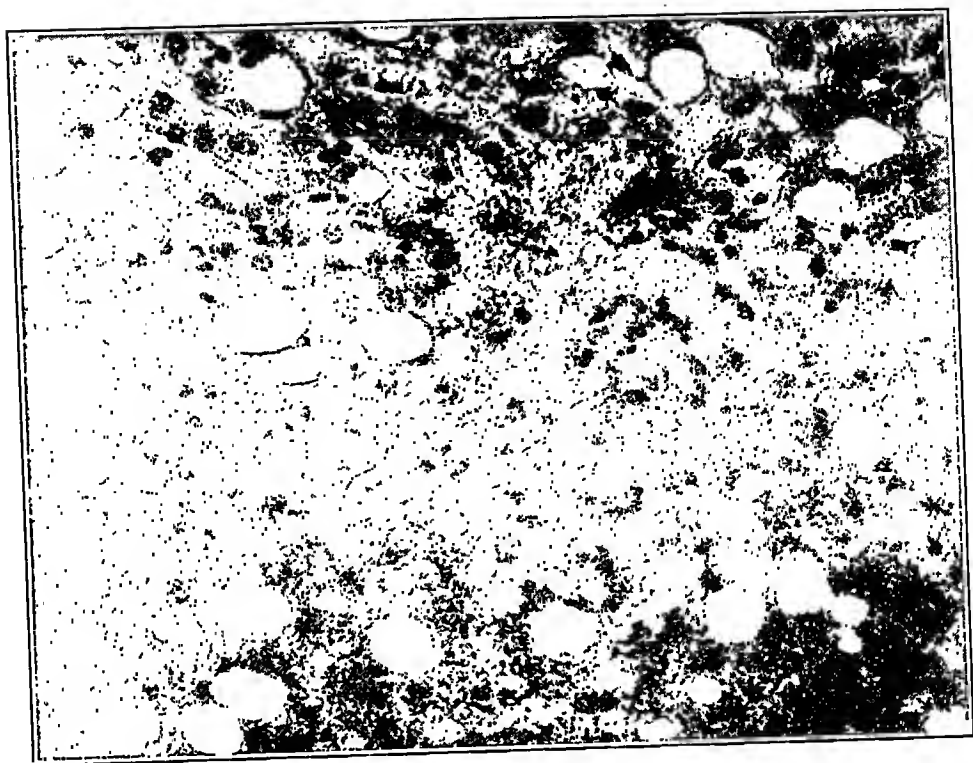


FIG. 1—Liver from animal O-14 given 4X animal dose orally. Marked congestion and diffuse fatty degeneration. Early necrosis in central portions of lobules. Older fatty infiltration.



FIG. 2—Kidney from O-14 (4X animal dose orally). Marked congestion and lipoidosis, particularly of collecting tubules in medullary rays of cortex. Sudan III stain. Dark tubules show extreme lipoidosis.

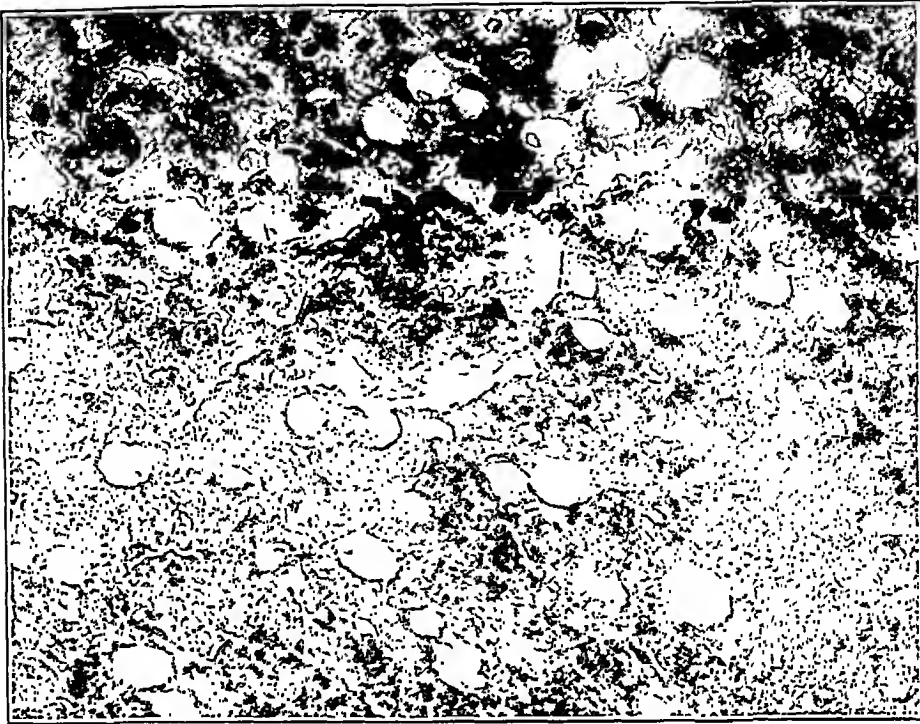


FIG. 3—Animal O-10. (3X animal dose given orally). Marked congestion, fatty degenerative infiltration and fatty infiltration of liver, with marked cloudy swelling and beginning necrosis of liver cells.

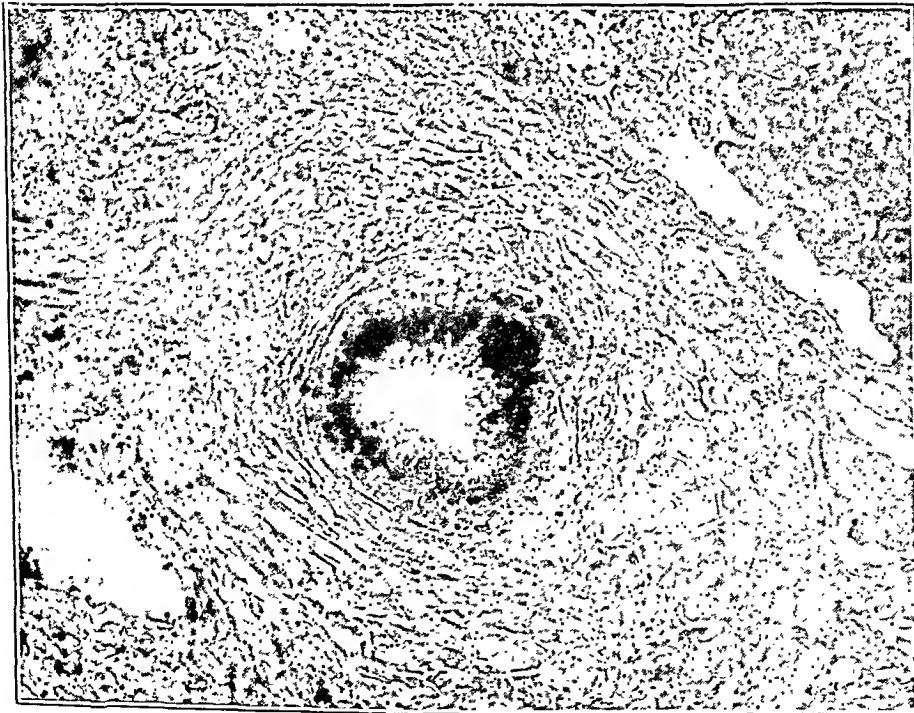


FIG. 4—Bile duct from liver of preceding, showing the marked lipodosis of epithelium. Sudan III stain.



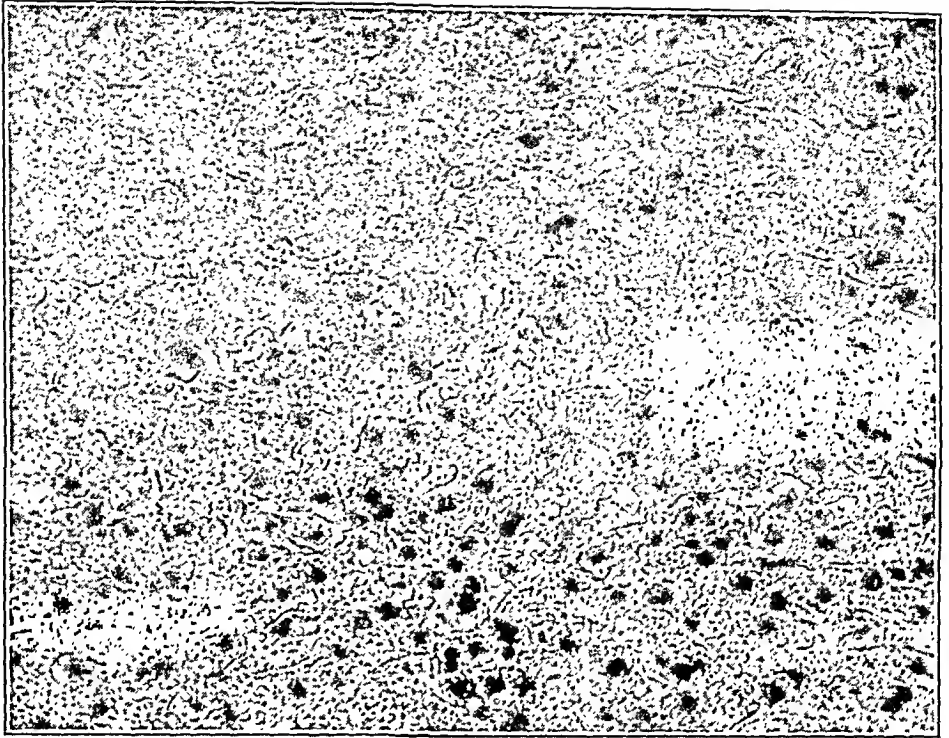


FIG. 5—Dog I-15. (3X animal dose intravenously; died). Liver showed marked congestion diffuse fatty degenerative infiltration and marked lipoidosis of bile ducts. Disintegration of liver cell nuclei.

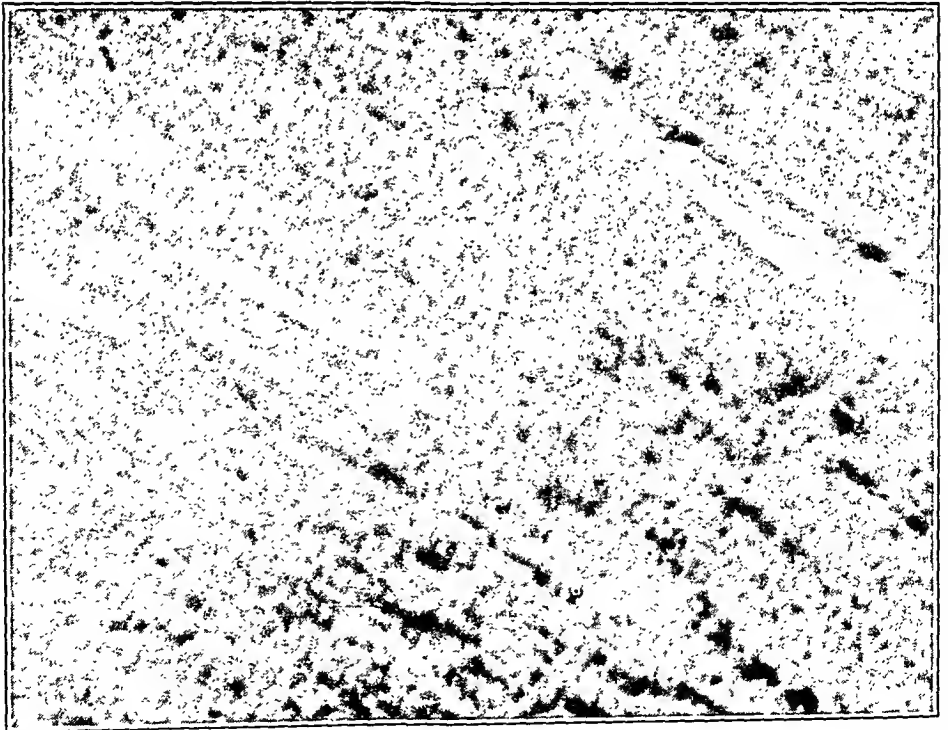


FIG. 6—Heart of animal in preceding figure, showing diffuse fatty degenerative infiltration and cloudy swelling. High power view of muscle fibers.

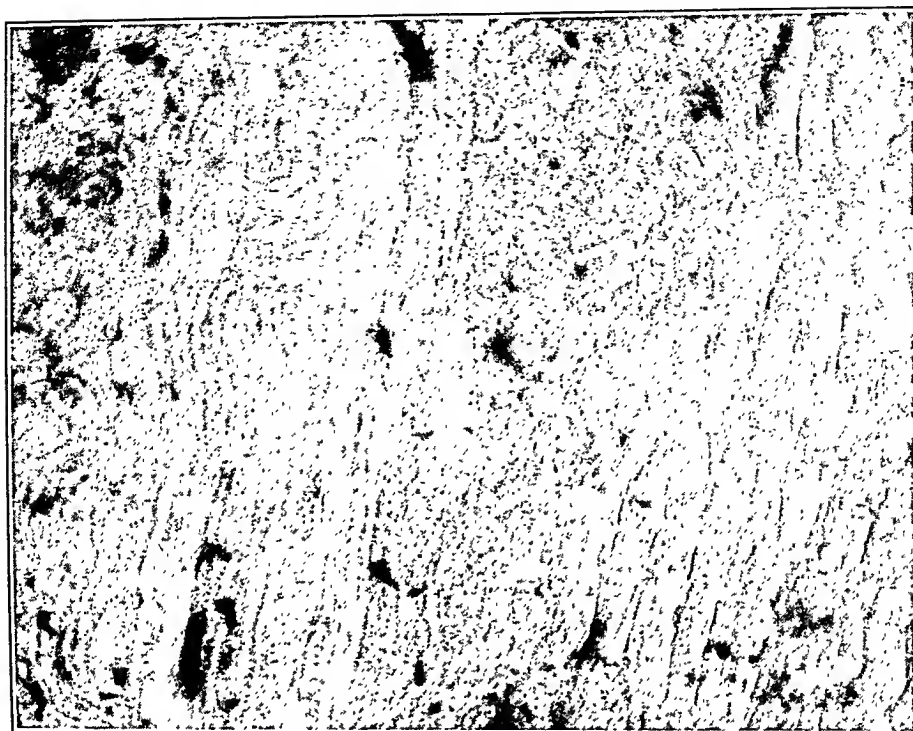


FIG. 7—Kidney from dog I-11 (Cholecystectomized. Usual dose given intravenously.) Kidney and liver showed marked congestion and lipoidosis. Sudan III stain.

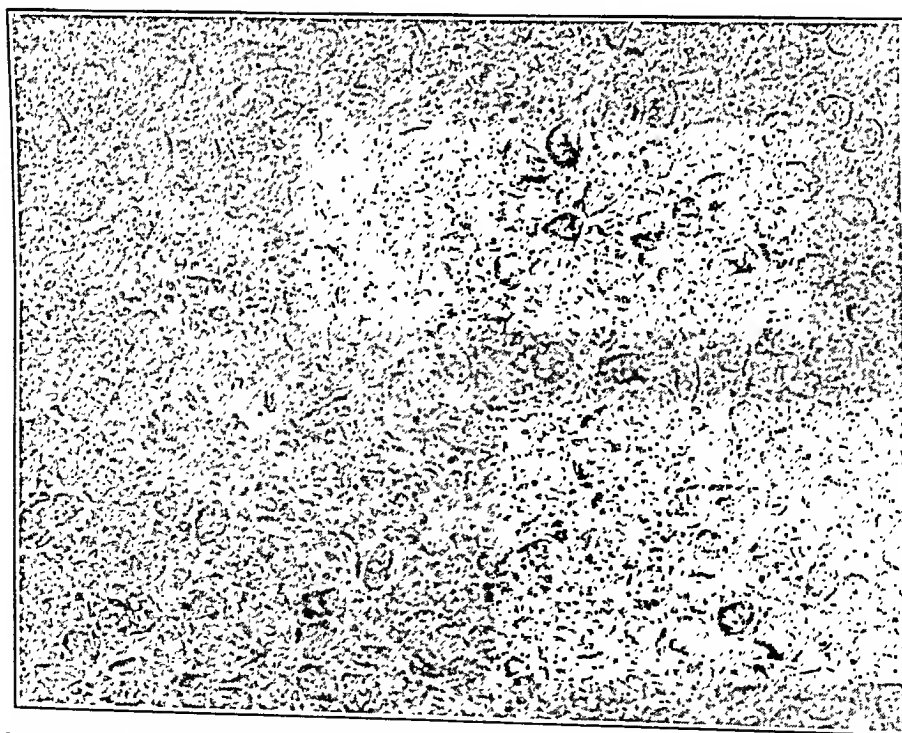


FIG. 8—Dog. I-10. (3X animal dose intravenously, causing death.) Liver showed advanced cloudy swelling and necrosis of central portions of lobules, marked congestion, diffuse fatty degeneration, and marked lipoidosis of bile-ducts.

# Further Observations in Cholecystography So-called Danger in the Use of Tetraiodophenolphthalein\*

BY MAURICE FELDMAN, M.D., *Associate in Gastro-Enterology, University of Maryland, Baltimore*

SINCE the advent of cholecystography numerous communications have appeared directing attention to the toxicity, as well as to the hepatic and renal lesions which have been attributed to the dye. (tetraiodophenolphthalein) utilized in visualizing the gall bladder. Graham and Cole, (1) as well as Ottenburg and Abramson, (2) were able to produce lesions in the liver and kidneys following injections of large amounts of the dye intravenously in animals. Rosenau (3) also points to the clinical and experimental work as indicating the possibility of liver damage following these injections, and cautions that these forms of dyes should be employed cautiously and only in moderate doses.

In as much as the oral method of gall bladder visualization is nowadays practiced to a large extent, replacing the intravenous method, it appeared important to us to determine whether a similar toxic effect or liver damage might also arise as the result of this method of administration. From numerous experiments performed by

Friedenwald, Kearney and myself (4) on animals following the oral administration of the dye, even when given in massive doses, it was observed that neither degenerative nor necrotic changes could be produced in the liver or kidneys.

In order to determine, however, whether pathological changes are produced in the human subject as an effect of the dye when given orally for purpose of cholecystography, an attempt was made to correlate certain clinical symptoms in a large series of cases following its employment.

On this account the following questionnaire was sent to twelve prominent radiological clinics.

State the approximate number of cases upon whom the gall bladder visualization test has been made.

In your experience, could death of any patient be attributed directly to the tetraiodophenolphthalein dye? If so, state number of cases and whether the dye was administered by the oral or intravenous method.

In your experience has the dye produced extreme toxic symptoms followed by inflammatory changes in the liver (hepatitis)?

State number of cases in which

\*From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland.

jaundice followed the administration of the dye.

State the cause of jaundice.

The results were as follows:

Total number of cases collected ..... 18,000

Death attributed directly to the tetraiodophenolphthalein none

Extreme toxic symptoms (Signs of hepatitis)..... none

Jaundice following the administration of the dye.. 3

Jaundice existed previous to the administration of the dye in one of my cases. This was caused by a stone in the common duct producing obstruction. In only two other instances of the 18,000 cases was jaundice noted following the use of the dye. In these cases a stone in the common duct was also observed at operation.

In many instances in our series jaundice existed previous to the administration of the dye, which was in no way intensified by the dye. A similar observation has been noted by others.

#### CONCLUSIONS

As the result of a collective investigation of 18,000 cases in which cholecystography was performed, the dye being administered by the oral route, the results uniformly indicate that this method is free from all danger; furthermore, there has been no evidence presented to indicate that any degenerative changes have been produced in the liver or kidneys by this procedure. The conclusions have been fully confirmed by the experimental findings on animals, already reported by Friedenwald, Kearney and myself (5).

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## Editorials

### *BENIGN GLYCOSURIA*

**I**T is usually the general practitioner who makes the discovery that a given individual has glycosuria, and such discovery is generally based upon a more or less crude use of the Fehling's test. If any reduction takes place, be it rapid or slow, slight or marked in degree, the decision is quickly made that glycosuria is present and the individual a diabetic. The physician is very likely to forget that other substances, conjugated glycuronic acid, alkapton, lactose, pentose, and excessive amount of uric acid or creatinin, may reduce alkaline copper sulphate solutions. He usually does not control the reduction by the application of other tests, and all too frequently he is not in a position to make a blood sugar examination. In the first place he is unable to tell whether glycosuria is actually present or not, and in the second place, should it be really present, he cannot tell whether the individual has true diabetes or a benign glycosuria. Of the latter possibility it is quite likely he has never heard. The unfortunate Fehling's-reducing patient, therefore, is labelled diabetic, and his life henceforth becomes an existence of care, anxiety and denial, and of all the unpleasant features that attend living on a diet. Or worse, insulin treatment may be instituted at once, with unfortunate results. If an applicant for life insurance, his application may be

rejected. The consequences of such errors in diagnosis may, therefore, be very serious, not only from a physical and psychical standpoint, but also as regards social and economic considerations. Yet it can hardly be doubted that in most communities there are individuals in this very situation of living as diabetics when they have no diabetes. In the first place it should be emphasized that non-diabetic glycosuria is of very frequent occurrence. Faber has stated that in an ordinary medical department the examination of the urine from all of the patients who have partaken of a meal containing much sugar will show glucose to be present in the specimens of urine in from 20-30 per cent of the patients. After an alimentary ingestion of larger quantities of glucose considerable glycosuria may be seen in 33 per cent, and even after the ingestion of starch glycosuria will occur in about 20 per cent. Holst made a study of 163 individuals rejected by life insurance companies as diabetics because of glycosuria and found that only 30 per cent were true diabetics; the remainder had benign glycosuria. When twenty-seven cases of the latter were studied over periods of from one to twenty-five years no other sign of diabetes developed, although the majority had given up any diet. By repeated examinations of the same patient he has demonstrated that year by year the administration of 50 gm. of glucose would give a blood

sugar rise to about 0.20 per cent, the patient showing constantly a harmless cyclic glycosuria. It may be difficult to distinguish between these cases and an early diabetes when the cyclic glycosuria is not due to a low threshold. Holst calls attention to the fact that when a patient lives on full normal diet without carbohydrate restrictions, an absolutely normal fasting blood sugar will almost with certainty rule out true diabetes. Should a cyclic glycosuria set in during the course of the day, it is due either to too low a threshold or to too great an alimentary rise, without in either cases denoting an abnormal metabolism, or having any serious influence on the future of the individual. Extensive studies of the glycosuric threshold, both in diabetics and in non-diabetics, carried out by Faber and others have shown that the glycosuric threshold varies in different individuals, but has a fairly constant position in the same individual. In the diabetic this position is independent of the duration of the disease or of the age of the patient. In normal individuals a low glycosuric threshold is simply an individual constitutional peculiarity, and, as far as he is concerned, is harmless. Such facts must be recognized by practitioners, and especially by those who examine for life insurance. The practical importance of a knowledge of benign glycosuria is very great for the individual concerned, and he must be protected from the dangers of an erroneous diagnosis of diabetes. Insignificant transient glycosurias must not be interpreted as diabetes. While the sugar threshold of a given individual is to be regarded as an inherent constitutional quality of the individual,

and varying considerably in different individuals, it may change under varying conditions. Thus an experimental glycosuria without hyperglycemia may be produced by the administration of phloridzin and a few other substances. Pregnancy is also a factor that influences the position of the threshold. Through numerous investigations it is now well known that glycosuria with normal blood sugar is not infrequent in Pregnancy. It has even been proposed to use this symptom as a diagnostic factor of early pregnancy. Its value in this respect is but little, since it is not a constant phenomenon in the pregnant, and may occur in the non-pregnant. Nevertheless, it is in itself a significant phenomenon in the light it throws upon the problem of the glycosuric threshold. Studies by Faber have shown that in some normal pregnant women the threshold may fall throughout pregnancy on a normal diet. The patients were usually sugar free in the mornings. The normal threshold was not reached until several weeks after parturition. Abnormal conditions in the blood sugar threshold, constitutional or due to changed conditions as pregnancy, may thus give rise to glycosuria without hyperglycemia, and such glycosurias may be permanent or transient. Some individuals are born to be glycosurics and show this phenomenon throughout life, just as others are born to alkaptonuria, pentosuria or some other peculiarity of metabolism. These peculiarities of the sugar-regulating apparatus are abnormalities of the constitution, but they do not constitute diabetes. Their lives may proceed regularly enough and comfortably enough if their peculiarity

is not discovered by some practitioner or examiner who labels it diabetes. Numerous cases of this kind have been studied for long periods, and the low glycosuric threshold has not been shown to exert any influence either upon the course or the duration of life. Inasmuch as diabetes is one of the best advertised diseases of man and has come into the mental limelight of the layman, the testing of urine for glucose is more and more frequently asked for and made. Glycosuria is, therefore, more and more frequently discovered, and incorrect interpretations of benign glycosuria as diabetes are correspondingly more frequent. It is increasingly important to insist that the diagnosis of diabetes cannot be based upon the symptom of glycosuria alone, but that accurate determinations of the fasting blood sugar must determine the diagnosis. This is just as important for the diabetic as for the non-diabetic. Inasmuch as the diabetic in many cases has no other clinical symptom than the glycosuria the fasting blood sugar determination is as necessary to his diagnosis as the negative results of this determination are to the non-diabetic. Mistakes in either direction are disastrous. If the fasting blood sugar is abnormally high the diagnosis of true diabetes should be made. When there is a normal fasting blood sugar, a number of determinations should be made at intervals of several weeks. In the meantime the patient should continue his regular diet with carbohydrates. If the patient for a long time has shown a normal fasting blood sugar, that is below 0.11 per cent, it is highly probable that the glycosuria is of benign character and not a sign of diabetes.

The determination of the type of glycosuria may then be carried out by determining several curves after the administration of carbohydrates. When a low threshold is found to be the only cause of the glycosuria, the latter may with certainty be regarded as benign. The problem is more difficult in the case of an alimentary rise of abnormal height. Benign glycosuria may be the result of an inherent deficient blood sugar regulation, and due either to an intrinsic low threshold or to an abnormally high alimentary blood sugar rise. In some individuals both conditions may occur, but more frequently a benign glycosuria is dependent upon too low a threshold. In 75 cases of benign glycosuria studied by Holst a low threshold was found in 22, an abnormally high rise in blood sugar in 15, and a combination of low threshold and high alimentary rise in 11; in 27 cases the type was not determined. Holst and Faber declare that in both cases, low threshold or high alimentary rise in blood sugar, it is a matter of individual peculiarity rather than of metabolic disease; and that in their experience they have never known a case which at first was definitely determined as benign to turn out to be a true diabetes. A cyclic alimentary rise may be present for years without ever changing into diabetes. It is, therefore, extremely important to the patient to have a correct differentiation made as to the nature of any existing glycosuria. Undoubtedly there are throughout the country great numbers of individuals with benign glycosuria who have been incorrectly diagnosed as diabetics, who have been refused life insurance, who have unfortunately been subjected to

the dangers of insulin treatment, or to rigorous and unnecessary systems of diets; and all of them suffering more or less from the psychical, social and economic results of the incorrect interpretation. In spite of the diagnosis and treatment they live on for years without showing any other evidences of diabetes. Would they not have been infinitely better off if at the beginning the glycosuria had been interpreted as a benign individual peculiarity and not as diabetes? Faber's Clinical Lecture\* upon this subject should be read by every practitioner.

#### *APOLOGY FOR DELAYED JOURNAL*

The delay in getting out the summer numbers of the *Annals of Internal Medicine* has been due to various conditions attending the change of publishers from a commercial firm to the

College. Various legal questions had to be settled, and the last number of the last volume, the June number, had to appear before the new volume could be begun. Difficulties are now apparently over, and all perplexing problems met by legal advice, so that the numbers should now appear without further delay. The September and October numbers are on the press and will be shortly sent out; the November number is out in galley proof, and by the first of the year the *Annals of Internal Medicine* should be on a regular schedule. The increase in subscribers for the new volume has been so great that the July number has been exhausted, and it has been found advisable to print 300 more copies. This fact in itself is very gratifying to the College.

\*Lectures on Internal Medicine, Knud Faber, Paul B. Hoeber, New York, 1927.



## Abstracts

*Dynamics of Histogenesis in Cardiac Repair.* The Role Played by Connective Tissue. ORMAN C. PERKINS and ADAM M. MILLER (Archives of Pathology, May, 1927, page 785).

These writers have studied the elastic tissue of the heart wall at different ages. They find that with increasing age, without other cardiac or other vascular lesions, there is an increase in the amount of elastic tissue in the different layers of the heart wall. In cases of arteriosclerosis in which the heart wall is damaged as the result of nutritional disturbances, the connective tissue of the epicardium, myocardium and endocardium increases in amount, the increase being characterized by the appearance of large quantities of elastic tissue. The amount of elastic tissue appears to be directly proportional to the damage suffered by the cardiac muscle. In toxic conditions with sudden effect on the heart, formation of elastic tissue does not occur in conjunction with the damage to the heart muscle, but in toxic conditions in which the attack on the heart is prolonged a marked development of elastic tissue takes place. The elastic tissue may be regarded as a compensatory mechanism in the heart wall when there has been slow damage to the cardiac muscle. They conclude from the evidence afforded by their material that collagenous fibers may be transformed into

elastic tissue in consequence of prolonged stress and strain on the connective tissues containing the collagenous elements. The elastic fibers are derived directly from collagenous fibers which are so situated that they are subjected to an active existence rather than a passive one.

*On Bile Stimulation of Pancreatic Secretion.* A. C. IVY and H. C. LUETHI (Proc. Soc. for Exper. Biol. and Med., June, 1927, page 837.)

Mellanby found that the injection of bile of an adequate reaction into the duodenum of the cat stimulates the pancreas, and that this was the case after ligation of the pylorus and bile ducts, and after atropine and ergotamine. He suggested that bile is the intestinal stimulus of pancreatic secretion, functioning by causing the elaboration and absorption of secretin. However, in his experiments bile may have caused stimulation by a local nervous mechanism that is not acted on by atropine or ergotamine. The present work was done on dogs. The investigators found that bile by stomach tube stimulates pancreatic secretion, but not invariably and to the extent that N/10 HCl does. Bile applied to the Thiry fistula of a pancreatic-transplant-Thiry-fistula preparation, stimulates the transplant occasionally, but not uniformly. Bile applied to a pan-

creatic-transplant - jejunal - transplant, preparation does not stimulate, whereas N/10 and N/20 HCl do. The authors, therefore, conclude that bile stimulates pancreatic secretion, but is not as potent as N/20 HCl; and that bile is an adjuvant, but not an essential alimentary stimulus of pancreatic secretion in the dog.

*Scarlatinal Nephritis Experimentally Induced in the Dog.* CHARLES W. DUVAL and R. J. HIBBARD (Proc. Soc. for Exper. Biol. and Med., June, 1927, page 876).

According to these workers the dog is not only highly susceptible to infection with *Streptococcus scarlatinae* but will develop regularly a severe and often fatal form of acute glomerulonephritis following the injection of the specific streptococcal toxin alone. The animals show no exanthem, but the lesions are regarded as corresponding histopathologically to the glomerular and acute interstitial scarlatinal nephritis of man. Eight young healthy dogs were injected with 5 mls each of filtered streptococcal "lysate" which had been prepared *in vivo* after the method previously described by the authors. Within 4-6 hours they developed symptoms of toxemia, and 24 hours later were extremely ill. The urine microscopically was bloody, and analysis showed quantities of albumin, granular casts, bile and blood. Two of the animals died on the fourth and 3 on the fifth day following the inoculation. The others survived, and though apparently well have continued to show, at intervals, albumin and casts in the urine. Sacrificed two months later, these animals showed varying degrees of

chronic diffuse nephritis. The lesions of experimentally produced nephritis with *Streptococcus scarlatinae* may be primarily glomerular or interstitial, the determining factor depending upon the character of the material employed. The glomeruli are first affected when the toxic principle alone is used, regardless of whether the injection is made intravenously or subcutaneously. On the other hand the primary interstitial form occurs in the animals inoculated with the living culture, and in which a generalized infection has resulted. The acute interstitial lesion is a focal infiltration of the intertubular tissues with cells of the lymphocytic variety. As a rule neutrophiles are absent or few in number; in more advanced lesions they occur, but are not as numerous as the lymphoid and plasma cells. Associated with the interstitial lesions are viable streptococci which are readily demonstrable in stained sections, and recoverable in pure culture from the fresh tissue. The absence of fibroblasts or any other evidence of stromal activity in the early interstitial lesion is of significance. This fact would indicate that the lymphocytic infiltration is a true reaction on the part of the host to the injurious agent and in no sense reparative. From this it may be inferred that acute interstitial scarlatinal nephritis of man is the same kind of reaction. In regard to the primary glomerular lesion in the dog, the streptococcus toxin affects especially the capillaries of the kidney tufts, producing various alterations in the whole glomerular structure. There are lesions in the wall of the capillaries which cause the formation of thrombi, in consequence

of which the vascular loops become greatly dilated, occluded and later adherent to Bowman's capsule. Other glomerular tufts become enlarged through the appearance of numerous endothelial cells in the lumina of the capillaries. Bowman's capsular spaces generally contain blood in the form of hyaline masses, also albuminous material and desquamating epithelium. Later, in the capsular spaces where hemorrhage has occurred, early epithelial proliferations ("crescent" formation) are noted. All these structural changes cause the glomeruli to undergo further and more serious alterations through replacement by fibrous connective tissue of the destroyed capillary loops. While tubular changes are not an early feature in either the glomerular or interstitial type of experimental scarlatinal nephritis, they occur later in the process and appear in the form of epithelial degeneration, especially of the convoluted portion of the tubules. The living cells become swollen through the presence of fluid, granules, fat and hyaline droplets. Often the lumen is filled with blood, desquamated epithelium, granular and hyaline casts. Macroscopically the acute lesions of experimental nephritis in the dog are recognized by increase in the size of the kidney, swelling of the glomeruli so that they project above the cut surface, and by pinhead and smaller discrete yellowish white foci in the cortical substance and by scattered hemorrhages throughout the parenchyma. The investigators conclude that the various types of glomerular and acute interstitial nephritis of human scarlet fever can be regularly produced in the dog with the culture

and with the pure toxic principle of *Streptococcus scarlatinae*, and that these experimentally produced nephritic lesions are alike in kind and variety to the acute scarlatinal nephritis of man. The complete analogy affords the opportunity of study of the acute lesions in their related sequence. Unfortunately the photomicrographs accompanying this preliminary report are very poor and far from convincing.

*Ein Beitrag Zur Frage der Milzhämolysen.* E. Lauda (Zeitschr. f. d. ges. exper. Med., Mai, 1927, s. 505). The hemolytic function of the spleen has been almost universally accepted, and this organ has been generally regarded as the seat of normal hemolysis for worn-out red blood cells, and also for pathological forms of excessive hemolysis. Many observations on splenic pathology, and especially the therapeutic results obtained by different workers through splenectomy in hemolytic icterus, have spoken in favor of an active splenic hemolysis. The present day teaching that this red blood cell destroying function of the spleen is manifested both as a normal function and under pathological conditions is based upon numerous pathological observations and animal experiments. Under a variety of conditions phagocytosis of red cells and deposits of iron-containing pigment occurs in the spleen; nevertheless, neither of these two facts can be taken as positive proof of an *active hemolytic* function of the spleen. If the spleen does possess an active hemolytic function there should follow, after its removal, an increase in the number of red cells. The results of experimental work in

this direction vary greatly; some authors have found after splenectomy at least a temporary increase in the red cells; others have had contradictory results. These experiments can hardly be regarded as conclusive. Of greater significance is the finding, reported by numerous observers, that red cell resistance is increased, at least temporarily, after splenectomy. Studies of the splenic vein blood, with reference to the problem of an active hemolytic function on the part of the spleen have produced results so divergent that they have not contributed decisively to the settling of the problem. Lauda has produced a new research aiming at its solution along the following lines: comparison of red cell counts in the splenic vein and in other regional veins; changes in morphology of red cells in splenic vein; differences in resistance of red cells from splenic vein and those from other parts of the body; and the bilirubin content of splenic vein blood. As a result of his investigations he concludes: 1. Exact determinations of the red cell count in the splenic vein of dogs are attended by insurmountable difficulties. Comparative determinations of red cells in splenic vein and splenic artery, and in veins of other regions offer no evidence in favor of an active hemolytic function on the part of the spleen. 2. The observations of Heeres and Buschen that morphological abnormalities occur in the red cells of the splenic

vein could not be confirmed. 3. No differences in the resistance of the red cells in the splenic vein and those of other veins either in the normal or the toluylenediamine-poisoned dog could be demonstrated. 4. The splenic vein blood, neither in the normal animal nor in the toluylenediamine dog, showed any increase in bilirubin values over blood from other regions of the body. Lauda's results are, therefore, contradictory to those of many other observers. They show, at least, that the question of an *active* hemolytic function of the spleen is still an open question, insofar as experiments based upon the examination of splenic vein blood with respect to number, morphology and resistance of erythrocytes and bilirubin content are concerned.

*Versuche über Inhalation von Insulin.* Arnold Palm (Zeitschr. f. d. gesam. exper. Med., Mai, 1927, s. 432). Since it had been suggested that insulin inhalation might be used to avoid injections, Palm made a thorough study of various spray methods of administering insulin, and came to the conclusion that there was no chance of its becoming a practical method. In the watery solution necessary for use as a spray insulin was largely or wholly destroyed, so that excessive quantities would have to be used in order to obtain an effective dose. The method is, therefore, costly and wasteful.

## Reviews

*Clinical Case Taking.* Supplement to Methods in Medicine. By GEORGE R. HERRMANN, M.D., Ph.D., Assistant Professor of Medicine, Tulane University, New Orleans. 90 pages. C. V. Mosby Company, St. Louis, 1927. Price in cloth, \$1.50.

This manual of case-taking is offered as a supplement to the author's *Methods in Medicine*, the Manual of the Medical Service of George Dock, published in 1924. It consists of diagnostic data arranged as logically as possible in the natural sequence of the history, physical and laboratory examination. The introductory paragraphs emphasize the value of complete case records and outline the general principles involved in their preparation and the most important points in the technique of case-taking. The necessary administrative data are given as a front page to the record. The circumstances and condition at entrance are then to be described. Following this the present illness is considered, and the special points to be emphasized in regard to the chief complaint are outlined. The more common conditions to be considered under each of the common symptoms are given in detail; and the special points to be emphasized when the present illness suggests system disease are shown. The system review is followed by the social history, past history, family and marital history; and the essential features to be stressed in each type of case are given. The physical examination is next outlined in detail; and items of especial importance in various types of cases indicated either by parentheses or especial paragraphs. The laboratory examinations are simply mentioned and references given to complete descriptions of the same in *Methods in Medicine*. The minimum total requirements for the various types of cases, including the desirable routine laboratory studies, are indicated. Directions are then given as to

tentative diagnoses and for further procedures that may be necessary in the handling of the patient. An Appendix contains outline figures showing the different habitus groups, outlines of organs, surface landmarks, region outlines, skin and segmental distribution. This manual of case-taking represents the highest ideals in the teaching of medicine, the inspiring of the student to the scientific attitude of mind, the honest complete study of the patient from all possible sides in the solution of the problem of his ailment. Only by such detailed and thorough methods of clinical approach can medicine be saved from the failures of ignorance and incomplete examination or from the slough of dishonest quackery. The student of character and mentality will comprehend the importance of such thorough and methodical examinations and will endeavor to become master of the details involved in a complete examination of a patient; the poor and lazy student will complain that such detailed outlines are beyond his time and ability, and are, therefore, idealistic and not practical. The author has answered this latter argument in his preface. We recommend this manual of case-taking to every medical student who wishes to get the best out of his medical training, and to be able to approach that great unknown, the patient's disease, with the confidence that only the knowing how to do it can give him.

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*History of Cardiology.* By LOUIS FAUGERES BISHOP, M.A., M.D., Sc.D., F.A.C.P. Formerly Professor of Diseases of the Heart, Fordham Medical School, New York City. Consultant in Diseases of the Heart, Lincoln Hospital, New York; and JOHN NEILSON, JR., B.S., M.D., Assistant in the Cardiac Clinic, St. Luke's Hospital, New York. With an Introduction by

Victor Robinson, Ph.C., M.D. 71 pages. 12 Portrait illustrations. Medical Life Press, New York, 1927. Price in cloth, \$5.00.

This interesting monograph on the history of cardiology sketches the development of our knowledge of the heart through three periods classed by the authors as the Pre-Scientific period, the Period of Scientific Investigation and the Period of Scientific Application. During the first of these periods the knowledge of the circulation and its disorders was very obscure, and circulatory phenomena were regarded with superstition or awe. Only a few of the ancient thinkers sought for some explanation of the beating of the heart, the pulse and other circulatory manifestations. Plato, while considering the heart in a more or less philosophical sense, vaguely hinted that the heart was the ruler of the arterial circulation. Aristotle believed the heart to be the source of the blood and that the blood in turn was the general nutritive fluid of the body. He thought that the beating of the heart and the pulsation of the vessels were due to the expansion of the blood within these cavities rather than to any active motion of the fluid itself. He did not consider the pulmonary arteries and veins as part of the circulatory system, but believed them to be wholly separate. He observed that the heart contained blood and not air, as was a common belief of the period. Praxagoras (300-400 B.C.) was the first to make a clear distinction between arteries and veins. He thought that the arteries contained no blood but a mysterious vapor; only the veins contained blood, and these were considered the main blood vessels, an error undoubtedly based upon the findings in the cadaver. His erroneous doctrines were accepted for several centuries. Erasistratus and Herophilus dissected the heart, the former naming the valves and chordae tendinae. Both thought there was communication between the arteries and veins, that the arteries were the active elements and the veins the passive. It was Galen (131-201 A.D.) who disposed of the old error that the arteries contained air. He believed that the arteries arose from the

heart and the veins from the liver; that diastole was the important active movement of the heart, and that the blood moved in both arteries and veins in the nature of an ebb and flow rather than in a continuous circulation. He recognized the importance of the muscular element in the heart and vessels, and drew the conclusion that since the heart would beat outside the body, the impulse for its contraction must originate within the organ itself. He was the first to describe aneurism of the aorta. In the period of scientific investigation the authors group Aegidius Carboliensis, the student of the pulse; Mondino de Luzzi, who described the heart valves with great accuracy; Leonardo da Vinci, who believed that systole was the important phase of the cardiac cycle; Sylvius, who first described the foramen oval; Winter, who studied the muscular functions and the valves; Vesalius, who destroyed the Galenic view of pores communicating between the two ventricles, although retaining his views of separate arterial and venous circulations; Servetus, who described the pulmonary circulation as separate from the system; Realdo Columbus, who is thought to have been the discoverer of the pulmonary circulation; Brissot, the reformer of venesection; Fabricius, the teacher of Harvey; Anthonio Cesaalpino, who first used the word circulation, and discovered the direction of the venous blood; and Harvey, who completed the discovery of the circulation. Following Harvey came Malpighi, the discoverer of the capillaries and the red blood cells; Brelli, who attempted to calculate the contraction power per unit volume of the cardiac chambers; Stensen, who studied the muscular contraction of the heart; Mayow, who showed that the object of respiration was the exchange of gases between the air and blood; Glisson, who studied the muscular contractions; Lancisi, who attempted a classification of cardiac disease and made observations on aneurism and cardiac syphilis; Morgagni, who is said to have recorded the first case of heart block; Lomer, with his experiments of transfusion and infusion; Keill, who made extensive studies on the force of the heart beat; Hales, the first to estimate blood

pressure; von Haller, who proposed the myogenic theory of the heart beat; and Senae, who published a work on the heart, its action and diseases. In the period of scientific application the authors place Auenbrugger, Corvisart, Withering, Stokes, Corrigan, Bright, Hodgson, Laennec, Bouilland, Poiseuille, Ludvig, Louis, Hope, Potain, Traube, Morrey, Gaskell, Engelmann, Kent and His, mentioning the especial contribution of each to cardiology. A final section is then devoted to "three recent cardiologists," Theodor Schott, J. M. Groedel and Sir James Mackenzie, with a description of their contributions to technical cardiology. The monograph is a most convenient resume of the high spots in the development of our knowledge of the anatomy, physiology and pathology of the heart, and of the practical application of this knowledge in the treatment of cardiac disease.

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*Cancer Control.* Lake Mohawk Conference, 1926. Report of an International Symposium Held under the Auspices of the American Society for the Control of Cancer, Lake Mohawk, New York, September 20-24, 1926. 336 pages. The Surgical Publishing Company, 1927.

This is an elaborate account of the Lake Mohawk Symposium, the expenses of publication being borne by the Harry M. Lasker Memorial Fund. It contains the purpose and plan of the meeting by George A. Soper, the greeting to the foreign guests by William H. Welch, and the response for the foreign guests by Sir Bland-Sutton. The reports of the executive sessions contain addresses by Bland-Sutton, W. Sampson Handley, Hartmann, Besard, Marie, DuBois, Reverdin, Maisin, Tribiger, Bastionelli, Blumenthal, Balfour, Greenough, Regaud, Bierich, Soper, Bloodgood, Ewing, Roussy, Murray, Wood, Leitch, deVries, Deelman, Dublin, Semken, Saltztein, and Lillienthal. While these addresses contain much of interest about Cancer Prevention and Control Propaganda in the various countries represented by the speakers, very little of scientific value was presented. It was a meeting of propagandists, rather than one of scientific students

of cancer, and, therefore, should be judged from this standpoint alone. In this respect they give valuable information as to how much has been accomplished in Europe and this country towards the prevention and control of cancer. The matters discussed were largely those of morbidity and mortality statistics. Radiological treatment also received attention from Greenough and Regaud. Ewing's article on the prevention of cancer is sane and sensible, and is by far the best and most practical address given at this conference. The lack of agreement on such vital points is very well shown, however, by a comparison of his paper with that of Balfour of Rochester, Minnesota. In his paper on "Cancer of the Stomach" he states that "the removal of gastric ulcers will contribute largely to the control of cancer of the stomach and should be included in the educational campaign of the Society." Ewing in his paper says: "Assigning 5-10 per cent of gastric cancers to gastric ulcers, the excision of ulcers may be given credit for the prevention of a small proportion of cancers, but at the cost of considerable mortality." Roussy's review of the "New Theories of the Origin of Cancer" will be of interest to medical readers and students. deVries analyzes mortality returns and concludes that "mortality returns give too favorable an impression of the prevalence of cancer in general, and probably also of some important forms of cancer (stomach and intestine). The figures for some external cancers may be considered as fairly correct. Autopsy and mortality returns together give us a fairly correct idea of the importance of cancer. Therefore, postmortem examinations and specification in mortality returns must be encouraged." Deelman's paper on "Mortality among Different Races" is of interest in showing that race apparently has no relation to cancer incidence. The papers mentioned are the most interesting and practical ones, although the whole volume should be read by all interested in cancer for the light thrown upon the mental attitudes of many of those interested in cancer propaganda. We have already in an editorial called attention to the formal resolutions

adopted at this conference, and their weak-kneed attitude regarding hereditary susceptibility in cancer etiology.

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*The Beaver: Its Work and Its Ways.* By EDWARD R. WARREN, S.B., Collaborator, the Roosevelt Wild Life Forest Experiment Station, New York State College of Forestry, Syracuse, N. Y.; late Director of the Museum, Colorado College. Monographs of the American Society of Mammalogists, No. 2. 177 pages, xiii chapters, 71 line cuts, 73 half tones, Bibliography. Index. The Williams and Wilkins Company, Baltimore, Maryland, 1927. Price in cloth, \$3.00.

This book gives in a simple and non-technical language a full account of the life and habits of the most interesting small animal common to the North American continent. It is a book for the general reader as well as for students of science, and will make an especial appeal to those medical

men who are interested in out-of-doors and in wild life. The first chapter gives a complete description of the animal and its different varieties, and this is followed by one on its ancestry and a description of the giant beaver. Other chapters tell in a most interesting manner the story of many observations on the intelligence of the beaver, the construction of beaver dams and lodges, canals, trails and landing places. Beaver meadows are described, the animal's food and methods of tree-cutting are discussed in detail. Other chapters are concerned with the general habits of the animal, its breeding and family life, its manner of swimming and walking, its voice, its diseases, enemies and parasites. All of these chapters are illustrated freely with most interesting photographs. Its relation to fish and to bird life are discussed. A chapter is devoted to beaver fur, meat and beaver farming. What a beaver does not do is also told. This is a good book for anyone's nature library.



## College News Notes

The protracted illness of Dr. John Lichty, Superintendent of the Clifton Springs Sanatorium and Clinic of Clifton Springs, New York, has made it impossible for him to participate during the past few months in the work of The College. Dr. Lichty as Regent and Chairman of the Committee on Credentials has, for a long time, rendered great service to The College. His full and early recovery is sincerely hoped for by all members of The College.

B. T. McGhie, M.D.C.M., who for the past seven and a half years has held the position of Medical Superintendent of Westminster Psychopathic Hospital, a Federal Institution situated at London, Ontario, has been appointed to the position of Medical Superintendent to the Ontario Hospital, Orillia, Ontario, and will, after November 1st, have charge of the care of mental defectives in the Province at that institution.

Dr. Edgar M. Green (Fellow, February 21, 1924), of Easton, Pa., has been ap-

pointed a member of the Board of Medical Education and Licensure, to fill the vacancy caused by the resignation of Dr. Walter Estell Lee, of Philadelphia, Pa.

Dr. James E. Talley (Fellow, February 20, 1924) was recently elected Vice President of the Philadelphia Heart Association.

Dr. Hyman I. Goldstein (Associate, January 1, 1921) has been appointed Chief of the Medical Diagnostic Clinic of the Mt. Sinai Hospital of Philadelphia.

### Obituaries

Dr. Frank Tyler Stephenson, Detroit, Michigan—May 14, 1927. Appendicitis. Elected a Fellow of The College July 24, 1919.

Dr. Clyde Fenworth Karshner, Grand Rapids, Michigan—June 10, 1927. Splenic Anemia. Elected a Fellow of The College December 27, 1919.

# Rich Liver Diet in the Treatment of Anemias With Reports of Cases

T. P. MURDOCK, M.D., F.A.C.P., *Meriden, Conn.*

**T**HIS paper is a report of six cases of pernicious anemia, four cases of secondary anemia, one case of atypical secondary anemia, and one case of Hodgkin's Disease treated by a diet rich in liver, after the method of Minot and Murphy (1).

Whipple and Robbins (2) have said: "Any person who works with standard anemia dogs, and observes the ease with which hemoglobin regeneration can be controlled by diet factors, comes to believe that many types of human anemia may be treated to advantage by diet control, rather than by other methods."

Prior to the Minot and Murphy paper of last year, very little consideration had been given to diet in the management of the anemias. Transfusions and iron and arsenic were used in the treatment of these cases. Following the Minot and Murphy report, however, much impetus was given to the dietary management of primary and secondary anemias.

The following cases were observed, either on the medical service at the Meriden Hospital, or in private practice. In all cases dilute hydrochloric acid was used, the usual dosage being a teaspoonful three times daily. In no cases was iron or arsenic given.

The diet as outlined by Minot and

Murphy was strictly adhered to in all cases of primary anemia, and in the severe cases of secondary anemia. The diet outlined in ounces for the benefit of patients is as follows:

Calf or beef liver, sweet-

bread, or kidney . . . . 4 to 8 ounces

Lamb or beef . . . . . 4 to 8 ounces

Vegetables (particularly

spinach and lettuce) . . . 16 ounces

Fresh fruit . . . . . 8 to 16 ounces

Milk . . . . . 8 ounces

One egg.

One ounce of fat made

up of butter and

cream.

In the moderately severe cases of secondary anemia, a diet which was arbitrarily called a modified Minot diet was used. With this latter diet the patient was advised to restrict fats and to take generously of liver or kidney, or sweetbreads, lamb, or beef, green vegetables, and fruits. The response to the diet was very much more rapid in the cases of secondary anemia than in the primary anemia.

Recently McCollum (3), Simmonds and Becker have reported their work with vitamin E. They conclude that liver fats contain large amounts of vitamin E and iron, and believe that the value of the liver diet recommended by Minot and Murphy lies in its content of vitamin E and of iron.

It is fair to presume that the real value of the treatment is in the use of liver itself, and that probably the future will bring forth something in the way of liver fats or emulsions to manage these cases. This is of value because it is not uncommon to receive complaints from patients who tire of the strict dietary regimen. If in the future these people are permitted to take a regular diet, and in addition liver fats, the problem will be made much easier, both for patient and physician.

The economic problem, always a great one in the care of people with pernicious anemia, has very largely been solved by the new dietary regimen. In the past with the prognosis eventually bad, it seemed hard to have to send these people repeatedly to the hospital for transfusion. The hospital had to be paid, likewise the donor, occasionally the physician, and all of this with a known hopeless prognosis. The dietary regimen would seem to be within the reach of all.

That the liver diet has a specific action seem to have been proven by the recent work of Murphy (4) and his co-workers. They have shown definite changes in the blood composition in cases of pernicious anemia, treated with a rich liver diet. In this work they report a definite increase in reticulocytes which occurs usually between the fourth and tenth days. This is associated with a decrease in the bile pigment concentration. Coincidentally there is an increase in the red cell count, and hemoglobin concentration, and a return to a color index of one or less than one. The liver diet did not produce any change in the non-

protein nitrogen of the plasma, although the protein of the corpuscles increased markedly.

#### REPORTS OF CASES

##### *Primary Anemia*

*Mrs. E. P.* Age: 37 years.

Admitted to hospital October 5, 1926. History of increasing pallor, and weakness of two months duration. Sickly, yellowish pallor of skin. Tongue smooth. Slight oedema of lower extremities. Gastric contents showed no free HCL. Gastro-intestinal X-ray series negative. R. B. C. on admission, 1,570,000, Hb. 30%, W. B. C. 7,600. Smear typical of primary anemia. Blood Wassermann negative. Spinal Fluid Wassermann negative. Cell count 6, Blood Nitrogen 36 mgs. Blood Sugar 105 mgs. Clinical Diagnosis: Primary anemia.

*Treatment:* Minot diet.

Dilute hydrochloric acid, 1 dr. T. I. D.

Patient showed almost immediate clinical improvement; headaches disappeared, she felt much stronger, lost all gastric symptoms, color became better. Discharged after thirty days in hospital with R. B. C. 3,550,000, Hb. 60%. Count two weeks after discharge, 4,580,000 with Hb. 90%. Patient looks and feels entirely well. Reported on March 1st as being entirely well. Hb. 90%. Had not been entirely adhering to regimen.

#### BLOOD PICTURE

Date.	R. B. C.	Hb.	W. B. C.
10/5/26	1,570,000	30%	7,600
10/7/26	1,880,000	30%	7,600
10/11/26	1,840,000	34%	12,400
10/14/26	1,940,000	35%	7,000
10/20/26	2,200,000	45%	4,800
10/18/26	2,660,000	45%	6,200
10/23/26	2,290,000	55%	5,500
10/26/26	2,120,000	65%	6,400
10/28/26	2,870,000	65%	5,800
10/31/26	3,480,000	55%	7,200
11/2/26	3,777,000	55%	5,800
11/4/26	3,590,000	60%	5,300
11/6/26	3,550,000	60%	7,800
11/20/26	4,580,000	86%	7,400

Mr. W. B. Age: 34 years.

Patient was first seen December 1, 1922 with the usual signs of pernicious anemia: indigestion, weakness, exhaustion, and sore tongue. R. B. C. 2,352,000. W. B. C. 3,600. Hb. 50%. Patient was transfused twice at that time.

In this case it was noticed that the patient apparently commenced to relapse and he was placed on rigid Minot diet. His response was almost immediate, with a marked increase in red cells, and hemoglobin. The last count showed a very definite improvement, not only subjectively, but in general appearance of the man and the blood picture.

*Primary Anemia With Central Nervous Symptoms*

Mrs. J. G. Age: 45 years.

Patient admitted December 29, 1926, complaining of generalized weakness, numbness and weakness in lower extremities; vague complaints referable to stomach. On examination patient was an undernourished, pale, prematurely gray woman. Large patches of brownish pigmentation over skin. Tongue red, and smooth.

Gastric analysis showed achlorhydria. Spinal fluid negative. R. B. C. 3,390,000, W. B. C. 5,200, Hb. 70%. Put on Minot's diet, Hydrochloric acid, dr. 1, T. I. D. before meals.

BLOOD PICTURE			
Date.	R. B. C.	HGB.	W. B. C.
12/29/26	3,390,000	70%	5,200
12/30/26	3,420,000	60%	5,800
1/3/27	3,080,000	51%	5,400
1/8/27	3,940,000	69%	5,200
1/10/27	3,600,000	70%	6,000
1/13/27	4,120,000	75%	6,600
1/15/27	4,000,000	85%	5,800
1/19/27	4,030,000	90%	6,200
1/22/27	4,380,000	90%	7,400
1/25/27	4,670,000	85%	7,800
1/29/27	4,040,000	80%	7,800
Date.	R. B. C.	W. B. C.	HGB
Feb. 9, 1923.	5,928,000		100%
April, 1923.	5,084,000	5,400	60%
June 6, 1923.	4,800,000	6,200	70%

Was seen again on June 5, 1926 with a history that he has been feeling tired for the

past month, and indigestion and weak feeling.

Date	R. B. C.	W. B. C.	HGB.
June 5, 1926	4,224,000	4,000	70%

June 8, 1926. Was given 475 c.c. of citrate of blood.

June 13, 1926. Was given 500 c.c. of citrate of blood.

Date	R. B. C.	W. B. C.	HGB.
June 22, 1926.	4,780,000	7,600	80%
July 13, 1926.	4,016,000	7,400	70%
Nov. 22, 1926.	3,200,000	7,000	70%

At this point patient complained of exhaustion, sore tongue, and headache, and was placed on rigid Minot diet.

Date	R. B. C.	W. B. C.	HGB.
Dec. 20, 1926.	4,608,000	4,800	80%
Feb. 14, 1927.	5,120,000	8,600	92%

Patient did very well, became stronger, gastric symptoms disappeared, color improved. No improvement, however, in power of legs nor in numbness. Paresthesia in legs still present on discharge. Stay in hospital was thirty-seven days.

*Primary Anemia.*

Miss A. S. Age: 42 years.

Entered hospital, February 7, 1927. Patient gives history of anemia of some years duration. Has been quite weak of late; breathlessness on exertion, dizziness.

On examination, patient showed typical findings of primary anemia. R. B. C. 2,370,000, W. B. C. 4,800, Hgb. 40%. Gastric contents showed no free hydrochloric acid.

Patient put on rigid Minot's regime-diet, and hydrochloric acid.

BLOOD PICTURE			
Date	R. B. C.	W. B. C.	Hb.
2/7/27	2,370,000	4,800	40%
2/9/27	2,320,000	4,600	42%
2/11/27	2,580,000	5,000	38%
2/14/27	3,090,000	4,400	40%
2/16/27	3,010,000	5,200	40%
2/18/27	3,090,000	5,000	40%
2/21/27	3,840,000	6,200	48%
2/23/27	3,220,000	5,800	44%
2/25/27	3,400,000	6,000	50%
2/28/27	3,660,000	6,200	46%

3/2/27	3,720,000	5,400	48%
3/4/27	3,890,000	5,400	50%
3/7/27	3,980,000	5,600	56%
3/9/27	3,980,000	6,000	52%
3/11/27	3,990,000	6,800	52%
3/13/27	3,990,000	6,800	60%
4/15/27	4,480,000	6,400	80%

Symptomatic improvement very rapid, appearance improved, strength returned, red blood count increased gradually, and on discharge, March 13, 1927 after thirty-four days in hospital, red blood count was 3,990,000. On April 15, 1927, R. B. C. 4,480,000, W. B. C. 6,400, Hb. 80%.

*Mrs. E. B.* Age: 42 years.

Was seen on the 24th of April, 1926 with the usual signs of pernicious anemia, exhaustion, swelling of feet, mucous membranes pale, and sore tongue. R. B. C. 3,360,000, W. B. C. 6,000, Hb. 50%. Patient was placed on Minot diet.

#### BLOOD PICTURE

Date	R. B. C.	W. B. C.	Hb.
5/22/26	3,320,000	6,200	70%
6/19/26	3,060,000	7,000	68%
7/24/26	3,180,000	7,400	60%
9/4/26	3,200,000	8,600	70%
10/9/26	3,840,000	6,800	70%

At this time patient was placed on Minot diet.

Date	R. B. C.	W. B. C.	Hb.
11/6/27	4,704,000	4,800	70%
1/8/27	4,720,000	7,800	85%
3/12/27	4,804,000	8,400	80%

In this patient it is seen that the response to medication prior to the use of the high protein diet was very slow. The improvement with the dietary management of the case however, was at once noticeable.

#### Secondary Anemia.

*Mrs. L. M.* Age: 27 years.

Admitted to hospital October 28, 1923. Has had recurrent attacks of rheumatic fever over a period of years, chorea in childhood. Came into hospital because of recurrence of rheumatic fever, and early symptoms of heart failure.

Patient showed marked pallor of skin and mucous membranes, several swollen tender points. Signs of early congestive heart failure. Heart shows signs of mitral stenosis,

and insufficiency. Blood count on admission: R. B. C. 3,320,000, W. B. C. 5,100, Hgb. 70%. Put on Minot's diet; no hydrochloric acid. Specific treatment for rheumatic fever.

#### BLOOD PICTURE

Date	R. B. C.	W. B. C.	Hb.
10/28/26	3,320,000	5,100	75%
11/6/26	3,720,000	8,700	65%
11/10/26	3,380,000	8,200	74%
11/12/26	4,220,000	6,800	72%
11/15/24	4,970,000	7,000	73%
11/24/26	5,520,000	7,800	75%

Red blood count went up quite rapidly, patient's general condition improved. Discharged in good condition, November 29, 1926. R. B. C. on discharge 5,520,000, Hgb. 80%. Stay in hospital, twenty-seven days.

#### Secondary Anemia

*Mrs. M. S.* Age: 37 years.

Patient entered hospital December 9, 1926 with history of bleeding from hemorrhoids for two months, or more. Had lost weight. On admission was very weak, pale, had frequent dizzy spells. Dyspnea, and palpitation on exertion, numbness, and tingling of extremities, swelling of ankle.

On admission R. B. C. was 2,470,000, with Hgb. 42%. Smear showed changes of a marked secondary anemia. Patient put on Minot's diet with hydrochloric acid. In spite of some continued bleeding from rectum, the red blood count went up to 3,680,000 on January 8, 1927. Hemorrhoidectomy performed January 10, 1927. Patient discharged January 12, 1927 with R. B. C. of 3,790,000. Felt quite well on discharge.

#### BLOOD PICTURE

Date	R. B. C.	Hgb.
12/9/26	2,470,000	42%
12/10/26	2,370,000	46%
12/15/26	2,630,000	46%
12/18/26	2,840,000	52%
12/22/26	3,150,000	54%
12/28/26	3,630,000	50%
12/31/26	3,290,000	58%
1/4/27	3,140,000	52%
1/8/27	3,680,000	54%
1/12/27	3,580,000	50%
1/14/27	3,790,000	50%

Mrs. L. H. Age: 46 years.

Patient admitted to hospital December 12, 1926. She was suffering from advanced congestive heart failure, showed marked oedema, was vomiting a great deal, and was extremely weak. Could take no diet at first. With digitalization, and diuretics, patient's condition improved. However, R. B. C. which was 2,570,000 on admission, was only 2,650,000 on December 23, 1926, thirteen days after admission. On latter date, Minot's regimen was started with hydrochloric acid dr. i, T. I. D. General condition improved still more rapidly, and red count mounted rapidly, being 4,140,000 on January 27, 1927, thirty-five days after introduction of the diet, and forty-nine days after admission to hospital.

#### BLOOD PICTURE

Date	R. B. C.	Hgb.
12/13/26	2,570,000	45%
12/23/26	2,650,000	50%
12/27/26	3,190,000	60%
12/31/26	3,200,000	62%
1/4/27	3,690,000	48%
1/10/27	3,480,000	45%
1/13/27	3,820,000	65%
1/12/27	4,040,000	60%
1/20/27	3,750,000	65%
1/24/27	4,080,000	70%
1/27/27	4,140,000	75%

Mrs. J. F. Age: 42 years.

Patient was seen on October 2, 1926 with a history of exhaustion, weakness of arms, constipation, some pain in left side of chest. Menstrual periods lasting seven or eight days; appetite poor.

The only positive sign was a slight enlargement of the heart. The pelvic examination which was done by Dr. James F. Miller of Hartford was negative for fibroid or malignancy. Blood Wassermann negative. Nonprotein nitrogen 22 mgs. in 100 c. c. of blood. Blood sugar 105 mgs. in 100 c. c. of blood. Urine—1018 acid clear, albumin and sugar negative. R. B. C. 3,200,000, W. B. C. 6,000, Hgb. 50%, Polymorphonuclears 67%, Large lymphocytes 9%, Small lymphocytes 24%.

Diagnosis: *Secondary anemia.*

Artificial menopause was produced with radium.

#### BLOOD PICTURE

Date	R. B. C.	W. B. C.	Hgb.
12/22/26	2,940,000	5,400	45%
Placed on Minot diet.			
1/20/27	3,800,000	7,000	55%
2/22/27	4,456,000	6,800	70%
3/24/27	4,712,000	8,000	78%

Clinically the patient has improved very much. She looks better. Color is very much better.

J. S. Age: 14 years.

Patient was admitted to hospital on December 30, 1926. The chief complaint at this time was respiratory embarrassment. He coughed some. The past history excepting the usual children's diseases was negative. He was undernourished. The positive findings were enlarged cervical axillary and inguinal glands, spleen and liver were palpable, there was a soft systolic murmur at the apex. An X-ray of the chest showed massive mediastinal enlargement. The blood Wassermann was negative. Blood sugar 88 mgs. in 100 c. c. of blood. Non-protein nitrogen 20.5 mgs in 100 c. c. of blood R. B. C. 3,820,000, W. B. C. 20,000, Hgb. 60%, Polymorphonuclears 74%, Small lymphocytes 19%, Large lymphocytes 7%. On January 1, 1927, one of the enlarged axillary glands was removed. Biopsy report showed typical picture of Hodgkin's Disease. The patient had several severe attacks of respiratory embarrassment. At intervals the temperature was elevated for several days. The patient has gradually grown worse. The following blood picture before and after Minot's diet is outlined below.

*Atypical Secondary Anemia.*

W. S. Age: 67 years.

Patient was seen on February 1, 1927 with the usual history of tiring easily, occasional attacks of dizziness. Past History negative except for rheumatism 20 years ago. The positive physical signs were: Skin and mucous membranes pale, soft systolic murmur at apex of heart, heart irregular.

## BLOOD PICTURE

Date	R.B.C.	W.B.C.	Hgb.	Polys.	Lrg.	Sm.
			%	%	%	%
12/30/26	3,820,000	20,000	60	74	7	13
1/5/27	3,460,000	17,200	70	87	8	5
2/16/27	2,980,000	15,000	70	74	11	15

At this point the patient was placed on a rigid Minot diet.

Date	R.B.C.	W.B.C.	Hgb.	Polys.	Lrg.	Sm.
			%	%	%	%
2/19/27	2,990,000	17,000	50	84	10	6
2/28/27	3,410,000	28,600	60	85	6	9
3/7/27	3,460,000	17,400	50	85	7	8
3/15/27	3,810,000	14,000	70	80	11	9
3/19/27	4,100,000	17,000	80	80	12	8
4/1/27	4,350,000	24,600	60	90	6	4

The very unusual thing about this case is that while the condition of this patient has grown worse, the blood picture under Minot's diet has improved very much.

Spleen and liver palpable. Left inguinal hernia. Wassermann negative. Blood Sugar, 120 mgs. in 100 c. c. of blood. Non-protein nitrogen, 28 mgs. in 100 c. c. of blood. R. B. C. 3,872,000, Hgb. 40%, W. B. C. 8,800. Polymorphonuclears 56%. Large lymphocytes 11%, Small lymphocytes 35%.

The patient was placed on Minot's diet, and dilute hydrochloric acid.

## BLOOD PICTURE

Date	R. B. C.	W. B. C.	Hgb.
2/22/27	3,900,000	8,400	60%
3/17/27	4,100,000	7,800	60%
3/25/27	4,160,000	7,000	65%
4/8/27	4,300,000	8,200	75%
4/29/27	4,456,000	11,200	70%

The smears showed changes in the shape and size of the red cells, and marked achromia.

Mrs. S. R. Age: 46 years.

Past History: Patient had gastro-enterostomy done in 1912. Hysterectomy for fibroid in 1917. She was seen for present condition on November 20, 1926. Her chief complaint was great weakness.

The positive findings were cyanosis of lips, finger tips, throat, and tongue. R. B. C. 3,352,000, W. B. C. 5,400, Hb. 68%. A definite change in the shape and size of the red cells was noted. Spectroscopic examination showed no methemoglobin. A diagno-

sis of pernicious anemia was made, and patient was placed on Minot diet.

## BLOOD PICTURE

Date	R. B. C.	W. B. C.	Hgb.
12/28/26	4,040,000	6,600	70%
1/18/27	4,504,000	7,200	68%
3/10/27	4,260,000	6,000	62%
4/11/27	4,800,000	8,600	75%

The patient has improved very much. Cyanosis and weakness disappeared. The patient is feeling very much better.

## CONCLUSIONS

1. While it is true that the number of cases in this series is certainly limited, the uniform success obtained in bringing up the blood picture together with the clinical improvement can not be overlooked.

2. The Minot and Murphy regimen seems to have a very definite place in the treatment of anemias, either primary or secondary. It is noteworthy that improvement in the blood picture is slow and gradual for the first three weeks or so, but thereafter, in favorable cases, it progresses rapidly.

3. It is probable that the real value of the treatment is due to the presence of iron and vitamin E in liver.

4. The economic question seems to have been solved by this method of treatment. This is particularly true in those cases which formerly required repeated transfusions.

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# Anemia of Pregnancy

BY V. C. ROWLAND, M. D., *Cleveland, Ohio.*

**I**N 1924 the writer reported (A. M. A. J., February 2, 1924) two cases of hemolytic anemia of pregnancy and reviewed the literature up to that date. At that time the condition as a clinical entity was entirely unfamiliar to the obstetricians of Cleveland and no previous case record was found. In the brief period since that time at least four cases have been recognized in Cleveland. These cases and the literature of the last three years are to be considered in the present report.

The clinical picture may be recalled as follows: An insidious onset of anemia in the latter weeks of pregnancy often not recognized till in the puerperium. Usually, however there are symptoms ante-partum of weakness, breathlessness on exertion, palpitation, headaches, dizziness, some edema of the feet and occasionally, an associated definite toxemia of pregnancy with albuminuria and hypertension. On account of the toxemia, the anemia may be overlooked if the blood is not examined. Labor may come on prematurely, is characteristically short and relatively painless. Post partum bleeding is scant. Still birth may occur, but a living child does not share in the anemia and develops normally.

Labor aggravates the anemia. The patient may go into collapse at once after parturition if the anemia is quite marked. Typically however, there is the rapid progression in the anemia in the first week or two following delivery. At times this course is quite slow so that a serious degree of anemia is recognized only after two months or more of supposedly simply delay in convalescence and returning strength.

The type of the anemia in the reported cases has shown a rather confusing variation and one of the most definite advances in our knowledge of the condition in the last few years is the definite division into two groups namely those that are hematologically secondary and those that are hematologically primary anemias. This was pointed out by Esch, who made the first complete study of the whole subject in 1917. He now insists that the two groups are quite distinct, and that no cases of the secondary or chloroanemia, even though of high grade, ever pass over into the pernicious type. The secondary types may persist many months or even years later, resisting treatment. For example, he reports a woman of 27 showing post partum, 34% Hemoglobin, 3,472,000 red cells, color index .5, who nursed her baby 11 months and two years post partum showed 30% hemoglobin, 3,145,000 reds and .5 color index. Naegeli also

\*Clinic at St. Luke's Hospital for the American College of Physicians, Cleveland, February 21-25, 1927.



describes the stubborn anemias of the chlorotic constitution. Normally however, these pregnancy anemias steadily clear up after the post partum period. Transfusion hastens convalescence but is hardly indispensable as in the pernicious types of cases.

The second group, namely hematologically primary anemias, usually present the blood picture of pernicious anemia with an occasional aplastic or atypical form as reported by Larrabee. The latter reported seventeen cases of anemia of pregnancy all of severe grade. Seven of these were of the secondary type and all recovered mostly without transfusion. Eight cases presented the pernicious blood picture and of four not transfused three died. Four recovered after transfusion. One case of the aplastic type died in spite of transfusion. One highly atypical case recovered after removal of a greatly enlarged spleen, repeated transfusions having been unsuccessful. In this case seven transfusions within six weeks, totaling 3700 c. c. of blood were used. The patient, however, had previously had recurrent endocarditis and pericarditis with albuminuria and edema. Larrabee's cases would also indicate that the primary type of the anemia occurred more frequently in primiparae similar to a toxemia with special involvement of the blood forming tissues (*Hematopathia gravidarum*), while the secondary type occurs more frequently after a series of pregnancies and other debilitating factors. In the primary form, a family history of hemophilia or an hereditary tendency to anemia may be an important predisposing factor as in some cases of

pernicious anemia unassociated with pregnancy.

Benda has made some special studies of the pathology in pregnancy anemias and reports a decrease in blood cholesterol in contrast to the usual increase in pregnancy and also at autopsy an atrophy of the suprarenals in contrast to the usual hypertrophy in pregnancy. On the basis of the hypocholesterolemia, Dorle and Sperling administered cholesterol therapeutically and report an increased red blood count and increased resistance of erythrocytes within a few hours both in experimental animals and in patients. They used .08 gram in milk three times a day.

Drexel reported a case having several practical implications. The patient was pale from the beginning of her pregnancy and at four months was hospitalized with a definite anemia and an acute pyelitis. The latter cleared up but the anemia progressed to 25% hemoglobin and 1,500,000 red cells. At six months a hysterectomy was done under spinal anesthesia. A rapid and good convalescence followed. In eight weeks, the blood showed 64% hemoglobin and 3,800,000 cells. The case is significant in the early onset of the anemia and in that the course was apparently uninfluenced by the urinary infection but entirely dependent on the pregnancy itself.

Schneider reported a case in a woman of 41, para III, with a history of hemophilia among the male members of the family. The patient developed an increasing anemia and was given intensive medicinal treatment but the anemia progressed to 40% hemoglobin and 1,920,000 cells by the

eighth month when pregnancy was terminated. Ten days later the blood picture was 60% hemoglobin and 4,200,000 red cells. Such cases, of course, strongly support the idea that the pregnancy produces the anemia by a direct toxic action upon the blood forming organs. Aubertin, who reported 53 cases from Paris clinics says that the pernicious anemia of pregnancy has never been known to clear up without actual emptying of the uterus. However, closely the anemia may resemble the ordinary picture of pernicious anemia, Esch repeats his statement of 1917 that no authentic case of recurrence independent of pregnancy has yet been reported.

The case reported by the writer in 1923 (with a red count of 900,000) has remained in excellent health and has had one normal confinement since that time. Her blood however, as counted on two occasions was slightly below the average count of a normal woman. The latest count on February 9, 1927, showed 4,650,000 red cells, 90% hemoglobin and 5,200 white cells. This case was definitely of the pernicious or primary type. The case reported below is definitely of the secondary type.

#### CASE REPORT

(Courtesy of Dr. Barney)

Mrs. M. S., age 31, para V, developed pallor and weakness in the latter weeks of pregnancy and presented herself for examination, which showed a hemoglobin 30%, a pulse rate of 120 settling down to 90 with rest. On August 27, 1926, she was transfused with 500 c. c. of the husband's blood (both husband and wife being of Group 4). There was no reaction of any consequence and the patient's general condition was

much improved except for some pain in the right side. On the morning of September 6th, 1½ ounces of castor oil and 10 grain of quinine were administered. The membranes ruptured spontaneously and, rather atypically, considerable bleeding followed. The cervix was dilated to 1 finger, temperature 37, pulse 94, respiration 20, foetal heart 150 to 178. The blood picture at this time, three days after the above transfusion of 500 c. c. of blood was as follows: Hemoglobin 45%; red cells 3,290,000; white cells, 9,000; index .68; Differential: Polymorphs 60%; Large monos 8%, Small monos 28%, Eosinophiles 3%. A Barnes bag was inserted at 7:55 and expelled at 9.27 P. M. Left occipito-anterior position. Delivery at 11.32 by low forceps operation. Pituitrin and ergotol were at once administered. The placenta was expressed but there was some hemorrhage and the uterus was packed to conserve blood. The pulse quickened to 114.

The uterine tape was removed the following day. The lochia remained normal. The temperature continued 37 for four days, then 38 for four days. The baby (2600 grams) was taken off the breast but thrived normally. Convalescence of the mother was satisfactory. On September 22nd, the blood showed hemoglobin 60%, red cells 4,352,000, white cells 11,200. The urine at no time showed more than a trace of albumin and few leucocytes.

The patient made a prompt convalescence and has remained well.

The diagnosis of the anemia of pregnancy is to be made mainly from infection, especially post partum infection and endocarditis including subacute bacterial endocarditis. In the latter leucocytosis, embolic phenomena and petechia are significant. In the pernicious anemias of pregnancy hemonhagic manifestations have been rather unusual. Epistaxis and an occasional purpura or retinal hemorrhage have occurred. Early in pregnancy, the symptoms of the anemia are often disre-

garded as part of the pregnancy. Aubertin states that the diagnosis is usually made late and that of his 53 cases 19 had initial counts of 1,000,000 to 1,500,000 and 3 below 500,000.

The newest phase in the etiology of this condition is the study of the blood groupings of infant and mother. Instead of being in the same groups as usual, they have in a number of instances been found to be in incompatible groups leading to the idea that hemolytic agents from the foetus were responsible for the anemia of the mother. Further statistical data are necessary in this interesting beginning. It can be obtained with very little additional trouble since the blood of the mother is usually typed in preparation for transfusion.

There are no important additions to the treatment of the condition. Transfusion apparently has not been used in Europe as much as in America. Aubertin refers to the subcutaneous injection of 30 to 100 c. c. of citrated

blood as the best treatment. With the present day technique in transfusion it certainly would ordinarily be preferred in America. In the puerperal aplastic anemias in which transfusion has failed one must rely on stimulants of the hematopoietic organs especially arsenic and iron. Clausser reports good results from the slow intravenous injection of colloidal antimony trisulphide in a concentration of 2.53%, stating that 16,000 normoblasts per c. cm. were observed after a single injection.

The important thing is to recognize the condition early so that the patient is not allowed to go into desperate condition. In the case reported a transfusion of 500 c. c. in the eighth month of pregnancy caused no disturbance whatever. The case however was rather mild and of the secondary type. In a severe and progressive case, termination of pregnancy should not be deferred too long because of the danger of collapse at parturition.

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# Hemolytic Anemia of Pregnancy with Reports of Cases

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**H**EMOLYTIC anemia of pregnancy is a specific form of anemia, occurring usually during the latter months of pregnancy, or during the puerperium.

Despite the fact that these women frequently show a definite blood picture, and the clinical manifestations of primary anemia, it would seem that this disease is a specific type of anemia of pregnancy, because if the patient survives the acute attack, the blood picture usually returns to normal, and apparently remains so. This latter fact definitely removes the disease from the heading of primary anemia.

The literature on the subject is not voluminous, and much work remains to be done. This is particularly true as to the etiology.

Very little is known as to the etiology of the subject. Adler (1) believes that there is a predisposition to the disease. This is doubtful in view of the fact that in about all of the cases reported, no previous history of anemia could be obtained, and many of the people have had no recurrences.

Rowland (2) believes that there is produced in the ectodermal cells of the chorion, a synctial hemolysin.

Larrabee (3) reported seventeen cases of anemia occurring in preg-

nancy. Seven of these had the blood picture of secondary anemia, eight had the blood picture of pernicious anemia, one the blood picture and clinical signs of aplastic anemia, and one atypical anemia.

Rowland (2) reported two cases in 1924. Both of these cases gave the true blood pictures and clinical signs of pernicious anemia.

Hoskins (4) reported a case in February of this year. The clinical signs and blood picture in his case were those of pernicious anemia. He believes the condition to be very rare in England, and not uncommon in Northern India.

The diagnosis of the condition is not always easy. The anemia from post partum hemorrhage or the anemia secondary to any obstetrical hemorrhage should not be confused with this condition.

The anemias associated with the toxemias of pregnancy probably present the greatest obstacles to the proper diagnosis of hemolytic anemia of pregnancy. However, blood chemistry determinations, retinal changes, and urinary findings will be helpful in eliminating the toxemias of pregnancy.

Some patients suffering from hemolytic anemia of pregnancy have slight

elevations of temperature, and the possibility of puerperal sepsis must be considered. Subacute bacterial endocarditis (5) with its associated anemia must be ruled out. Blood cultures in both of these conditions will be helpful.

Given a case of progressive anemia, either with the blood picture of primary anemia, or one approaching it, and one which cannot be classed as secondary to any other cause, hemolytic anemia of pregnancy should be borne in mind. If to these facts are added the history of an easy or spontaneous labor with little or no bleeding, the diagnosis should be easily arrived at.

On the whole the outlook in this condition is good. Certainly it is not as bad as the older writers believed it to be. If the patient recovers from the so-called acute or active stage of the disease, the outlook for complete recovery is good. However, there seems to be a difference of opinion as to the possibility of recurrences of the disease with subsequent pregnancies. I believe that there is a very great probability of the disease recurring during subsequent pregnancies, and that this possibility should be given very serious thought by obstetricians. In one of the cases (Mrs. D.), reported below, it seems probable that the illness of 1920 occurring during pregnancy, and following delivery while undiagnosed as such, was hemolytic anemia, and that the attack in 1926 during a subsequent pregnancy was a recurrence.

The treatment until the present time has been transfusion in the severe cases. In the milder cases, many of them will respond to the administra-

tion of iron and arsenic, and the usual methods of treatment of mild anemia.

I am sure that in the future many of these cases will be successfully managed with the Minot and Murphy (5) high nucleo-protein diets. In one of the cases (Mrs. P.), reported below, the patient was placed on a high nucleo-protein diet after leaving the hospital, and the response was very gratifying. It would seem that this plan of treatment should take a prominent place in the management of these cases in the future.

#### REPORTS OF CASES

*Mrs. P.* Age-32 yrs. Primipara.

*Family History*—Father, mother and three sisters living and well.

*Past History*—Negative.

Patient was delivered by Dr. J. E. Stoddard on January 18th, 1926. Labor was long, and difficult, and forceps were used in delivery. Twelve hours later, patient had slight elevation of temperature. Patient was seen in consultation with Dr. J. E. Stoddard on February 11th, 1926, twenty-four days after delivery. She complained of feeling tired, and of some headache. Face slightly oedematous, mucous membranes pale, pulse rapid. R.B.C. 2,580,000 W.B.C. 8,400 Hb-50%. Polymorphonuclears—56%. Small lymphocytes—40% Large lymphocytes—4% Blood culture negative. Urine—1010, acid, clear, albumin small precipitate, sugar negative, occasional white blood cell. A diagnosis of hemolytic anemia was made, and patient was placed on iron and arsenic.

Subsequent blood counts were as follows: June 10th, 1926, R.B.C. 4,032,000 W.B.C. 8,000 HB. 70-80%. August 12th, 1926, R.B.C. 4,704,000 W.B.C. 4,600 Hb. 75%. Patient was placed on a high nucleo-protein diet. The blood count on September 2nd, 1926, was R.B.C. 5,028,000, W.B.C. 7,800, Hb-75%. November 2nd, 1926, R.B.C. 5,110,000, W.B.C. 7,600, Hb-90%. Reports from the patient since that time are that she is doing well,

and has not had any symptoms of recurrence.

*Mrs. D.* Age-26 yrs. Multipara.

*Family History.* Father, mother, brother and sister living and well.

*Past History.* Influenza in 1918. Patient gave history of kidney trouble during first pregnancy. This occurred in 1920. Following delivery, patient was anemic and this condition cleared up very slowly. Blood count which was done at this hospital, showed R.B.C. 2,400,000, W.B.C. 5,200, Hb-40%. It was believed at that time that patient had an anemia associated with a kidney disease. In all probability this was a true hemolytic anemia of pregnancy.

Patient was delivered on March 6th, 1926 by Dr. I. S. Otis. On March 18th, 1926, when patient was seen in consultation with Dr. Otis, she complained of exhaustion, headache, and ringing in ears. Patient was pale, head oedematous, conjunctivae, tongue, lips, and pharynx pale. There was a soft systolic murmur at the apex, blood pressure 110 over 60, liver and spleen palpable, R.B.C. 1,665,000 W.B.C. 6,600, Hb-40%. A diagnosis of hemolytic anemia of pregnancy was made, and transfusion advised. During this procedure, the needles became obstructed, and the transfusion was very unsatisfactory. On March 21st, 1926 the blood count was, 2,240,000, W.B.C. 6,800, Hb-50%. Polymorphonuclears-66% Small lymphocytes-27%, large lymphocytes-4%, Transitionals-3%. The patient was placed on iron and arsenic, and was discharged on April 10th, 1926. The blood count at this time was 3,300,000, W.B.C. 6,800 Hb-60%. A report since discharge is that she is doing very well.

*Mrs. E. M.* Age-32 yrs. Multipara.

Patient was seen in consultation with Dr. H. L. Peters, and Dr. H. W. Waterhouse. The patient complained of weakness, ring-

ing in ears, dizziness. She was taken ill on December 12th, 1924 with what was thought to be an influenzal infection. She was in the ninth month of her pregnancy. At that time she complained of weakness, headache, and dizziness. She was afebrile. On January 17 she was delivered of a baby. The labor was short, and with minimum amount of bleeding. Her convalescence was slow.

When examined on February 13th, 1925 she was pale, mucous membranes were pale, there was a systolic murmur at the apex, the liver and spleen were palpable. The Wassermann was negative. The R.B.C. was 1,600,000 W.B.C. 5,200, Hb-33%. There was a change in the size and shape of the red cells.

A diagnosis of hemolytic anemia of pregnancy was made. The patient was transfused, but the response was not marked, and transfusion was repeated one week later. Her condition improved at once.

A blood count which was done on March 14th, 1925 showed R.B.C. 4,100,000 W.B.C. 6,200 Hb-80%. May 19th, 1925, R.B.C. 4,944,000 W.B.C. 6,600 Hb-85%. July 9th, 1925, R.B.C. 5,464,000 W.B.C. 6,200, Hb-95%. February 1st, 1927, R.B.C. 5,318,000 W.B.C. 11,100 Hb-90%.

#### CONCLUSIONS

*1st.* Hemolytic anemia is a specific anemia of pregnancy with the blood picture resembling the blood picture of pernicious anemia.

*2nd.* The condition is likely to recur with succeeding pregnancies.

*3rd.* High nucleo-protein diets should be given a thorough trial in the management of this disease.

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# Early Diagnosis of Gastric Carcinoma\*

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THE seat of a large percentage of carcinomata is the stomach. For example, Reiche's Hamburg statistics show that 50.2 percent. of all cancers are gastric (1). The limits of this paper will not permit of a full discussion of the nature of carcinoma. It may be pointed out that the hypothesis of Dr. Guy and Mr. Barnard (2) that cancer is due to an ultra-microscopic, extrinsic virus, requires further confirmation before it can be accepted, since "it has not yet been possible to produce the disease with artificial culture of it." The researches of these investigators, however, aroused intense interest in the etiology of cancer. W. Blair Bell, who has given much attention to the specific character of malignant growths, claims that "malignant neoplasia is a specific growth process in that it is a revision on the part of the starving cell to the nutrient seeking proclivities of its ancestral type, the chorionic epithelium. (3) It may be, however, quite fairly assumed that the essential nature of cancer and its specific cause or causes are still unknown.

There are certain predisposing causes, which are universally recognized and should be kept in remembrance. Welch, who analyzed 2,038

cases of cancer, found that 75 percent. fell in the fourth, fifth and sixth decades of life. About 4 percent. of the cases occurred under the age of 30. This noted author gives the sex relationship as five males to four females.

Opinions are divided as to the influence of heredity. Warthin has stressed the frequency of occurrence of cancer in certain families. As a family disease, carcinoma of the stomach occurs in less than 15 per cent. of the cases. Cancer may develop in ulcer, but just how frequently is uncertain. Statistics vary widely; in the writer's opinion, not more than five per cent. are of this origin. Prolonged irritation due to alcohol or chronic gastritis may act as a predisposing factor. Repeated slight trauma to the epigastrium, as in certain occupations, may rarely be followed by carcinoma of the stomach.

Willy Meyer (4) has well said that clinical efforts should always be directed toward recognizing a precancerous state, and then aborting or excising it, as the case may be, and this applies to carcinoma of the stomach as well as involvement of other organs, although perhaps less directly. Bloodgood (5) states: "Cancer never begins in a healthy spot." Says W. J. Mayo: "No one has yet seen a cancer of the skin or visible mucous mem-

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brane of the body, which was not preceded by some form of chronic irritation. Investigation of the inner surfaces of the body reveals the same conditions always preceding cancer." It is quite probable that many cases of cancer of the stomach terminate in spontaneous recovery in this preliminary stage, which is occasioned by numerous cancer-inciting factors. The recognition of the precancerous states is here assumed to be an important factor in cancer prevention, since it affords an opportunity to "blight" the disease at its origin. Sokoloff (7) claims the leukocytic reaction may be the causal factor in malignant invasion of the tissues. A connection between this process and an increased polymorphonucleosis, as well as a diminished lymphocytosis is evident.

The early diagnosis of cancer of the stomach is not free from difficulty, although usually possible with those clinicians who will employ modern investigational methods without delay in the presence of any suspicious features. At the commencement of cancer proper, only the mucosa and submucosa are infiltrated, with gradual extension to the peritoneum, hence to wait until a palpable mass, or a localized induration even is detectable to palpation is to permit the opportunity of making an early diagnosis to pass, in most cases, at least. The same is true, if the physician procrastinates until there is marked anemia and loss of flesh and strength. Again, to wait for evidences of dilatation of the stomach with obstructive vomiting, would upon laboratory investigation reveal an advanced lesion.

The situation of the growth is important, since the symptoms vary somewhat with the portion of the stomach affected. According to Paterson (8), the growth is situated at the pylorus in 71 percent. of the cases, in the lesser curvature in 14 percent., and at the cardiac orifice in 5 to 10 percent. Rarely, the wall of the stomach is infiltrated throughout its whole extent.

When symptoms of gastric indigestion tend to persist despite approved treatment, carcinoma should be suspected, if the patient is in the fourth, fifth or sixth decade of life. The onset of gastric symptoms, which will be detailed later, in a person over forty, previously free from such features, together with evidence of impaired motility, and the constant absence of free hydrochloric acid as well as the presence of occult blood persistently and constantly in the stools, would strongly confirm suspicion of this disease.

The gastro-enterologist who habitually employs the stomach-tube recognizes gastric cancer earlier than the general practitioner, so helpful is a systematic examination of the gastric contents, when interpreted with the clinical symptoms. The latter should, however, use this appliance routinely in cases in which the slightest grounds for suspecting carcinoma exist; he should ever keep in remembrance the fact that gastric cancer soon passes beyond the stage in which surgery is effective. A thorough X-ray study, to which reference will be made hereafter at length, should be undertaken quite early. Again, evidence of impairment of the motor functions of the

stomach is an early finding, particularly if the growth is located at or close to the pylorus.

Certain local manifestations set in early, as a rule, *e.g.*, vague discomfort and uneasiness after food, in persons above forty years of age; this is the earliest symptom as a rule, but soon gradual loss of appetite, often with dislike for meats, and nausea, as well as eructation and more rarely epigastric pain, which shows a progressive tendency, appear. The pain may be dull and boring, but sometimes lancinating in character. The onset of pain is often determined by eating. Again, pressure may elicit definite pain in incipient carcinoma of the stomach. The pain may, however, be absent in early cases, and the same is true of all other local features, the picture being composed of the general symptoms only. Such cases are not as a rule recognized until pretty far advanced. Cancer may occur in the course of cases of long standing indigestion, so that such a history should not be allowed to disguise the diagnosis. Vomiting, especially of "coffee grounds" material, emaciation, and secondary anemia occur later, hence do not belong to the stage we are endeavoring to depict.

Cases, however, are met with in which loss of strength and weight with slight anemia were the first symptoms to attract attention. In these instances, the disease may reach an advanced stage before it is suspected on account of the appearance of local symptoms. Such cases have, therefore, usually passed beyond the hope of surgical relief when first recognized. It is to be recollected that cases which

begin by showing gastric symptoms first, also manifest among early features progressive loss of weight and strength, as well as an appreciable increasing degree of anemia.

A palpable tumor is in rare instances compatible with complete extirpation, and in exceptional instances a small palpable mass first directs attention to cancer. In carcinoma of the cardia, the symptoms are ill-defined, but difficult deglutition is often the earliest sign, merging slowly into oesophageal obstruction. Eructations are more common than when other parts of the stomach are the seat of the disease.

I would strongly advise an application of the investigational methods of examination, more particularly the X-ray and fractional analysis of the gastric contents in any case with active or indefinite gastric symptoms lasting one month unabated, and if the patient be in the cancer bearing period of life. Again, if these prove negative at the first thorough examination, they should be repeated at intervals of a couple of weeks.

As pointed out above, occult blood in the feces when constant and persistent, is quite suggestive of gastric carcinoma, and it is often encountered early in the disease. This finding is also met within gastric ulcer, although intermittently, as a rule. A marked decrease in free hydrochloric acid in the gastric contents is one of the earliest signs. Soon it disappears in the vast majority of instances. When present it therefore becomes rapidly less and less.

The fractional test meal extraction as introduced by Rehfuess is to be em-

ployed in these studies, so that the amounts of free hydrochloric acid and total and combined acidity are estimated at fifteen minutes intervals of time until the stomach shows no evidence of food following the ingestion of a test meal. The results of the fractional analysis can be plotted in curves, which may include the amount and nature of the gastric contents and secretion, but as pointed out by Relhuss and Hawk (9) "there is no definite curve in gastric cancer or ulcer, or for that matter any of the gastric conditions." Lactic acid is present and butyric acid is also common. In my view, the gastric contents obtained after a test-meal show fairly constant and characteristic findings by the fractional method on chemical examination.

It is well known that notable diminution in the hydrochloric acid also occurs in chronic gastritis, hence this finding must be interpreted with respect to the associated features. Microscopically, yeast fungi and sarcinae are frequently found in the gastric contents and a large non-motile bacillus, the Boas-Oppler, may be recovered therefrom after the disappearance of the free hydrochloric acid, in this disease.

The X-ray is one of the best, if not the best method, for early detection of a cancerous lesion in the stomach wall, which involves the exact determination and localization of the filling defect. The roentgen study may show merely changes in the rhythmic peristaltic waves to suggest pathologic changes in the stomach wall. Not less than 98 per cent. of all cases are recognizable

by means of X-ray according to Dr. Pfahler's statistics, while Taylor and Mallor found the X-ray gave a positive diagnosis in 96.8 percent. of 182 cases. Hurst (10) is of the opinion that a skilled radiographer can show an abnormality of the stomach in 100 percent. of cases of malignant diseases, and he strongly urges that the doctors send their patients early to the radiographer. An early positive diagnosis is rarely possible in cancer of the stomach, without the aid of the X-ray. It is not claimed here that the roentgen study always reveals carcinoma of the stomach, while it is still in the operable age, but it is of the highest value, if interpreted in relation to the clinical symptoms of the case. Whilst the greatest advance in diagnosis lay in thorough and accurate X-ray examination, it would be unwise to rely on the X-ray findings alone. We should not fail to employ the laboratory methods in all suspicious cases, since they are fully justified by most important findings, in some cases, at least. On the other hand, Christian (11) "has the impression that the early diagnosis of cancer of the stomach, in the sense of recognizing it in the stage when it is small locally, and particularly before it has metastasized, is still almost an impossibility, using methods at present available." In his statistical studies few cases of cancer are unexpectedly revealed by X-ray examination in patients whose full histories and systematic general physical examinations are recorded. J. W. Hunter (12), however, regards Christian's view as somewhat immature and thinks furthermore, that there is much to be said

of the negative roentgen diagnosis of cancer of the stomach. In my view Hunter is quite right in assuming that in the great majority of cases a negative diagnosis of carcinoma of the stomach is of value. Again, in my experience, an X-ray after the barium test meal has led to an earlier detection of cancer than would have been possible without this aid. The point I would particularly stress, however, is that the physician cannot afford to neglect a single one of the many bountiful resources at his command.

Peracchia (13) found the Botelho test for cancer positive in 84 per cent. of 172 serums from cancer patients, but only in 7 percent. of 103 patients without malignant disease. He prefers Botelho's simplified second method. The serum is treated with ammonia and nitric acid, after which addition of an iodine-iodide solution causes precipitation. This disappears in normal serum on adding a little more of the solution, but with cancer serum it increases and lasts. Moorehead (14) emphasizes venous thrombosis as a sign of early carcinoma of the stomach and cites four illustrative cases.

If gastric symptoms prove resistant to acceptable, dietetic, hygienic and medicinal measures, in cases in which the roentgen study is inconclusive, an exploratory operation is to be advised for purposes of diagnosis and with the hope that if cancer be present, it will be found to be operable. Whilst gastric carcinoma is usually a primary disease, it may rarely be secondary to involvement of the liver, gall bladder, duodenum, pancreas and intestines, in

which instances the early recognition of the gastric growth is less important since surgical treatment would be of no avail.

#### DIAGNOSIS

Notwithstanding the frequency of occurrence of cancer of the stomach, out of 2,345 patients who suspected they had cancer, examined by eleven clinics in Detroit, only three cases of stomach cancer were diagnosed positively, presumably for the reason that these examinations could not be complete (15). It will readily be seen from these results that the early recognition of carcinoma of the stomach demands close and thorough study.

In no other gastric affection is a painstaking, searching history of so great importance as in cancer. The precise mode of onset and character of the accompanying symptoms, both local and general, are to be noted in detail. It must be recollected that 75 per cent. of the cases occur between the ages of 40 and 70 years of age. The words of Hale-White are pertinent here: "If symptoms of serious chronic gastric indigestion first appear after the age of 40, organic disease of the stomach should be strongly suspected."

The early symptoms are vague discomfort after food, impaired appetite, eructations, rarely epigastric pain and loss of strength and should suggest cancer of the stomach, and lead quickly to thorough laboratory investigations. Clinical study of the patient, while important, is not the most vital step toward a diagnosis, but accurate laboratory investigations, hence the latter should be instituted early and repeated at brief intervals of time in suspicious

cases. A marked diminution or total absence of free hydrochloric acid and the presence of occult blood in the feces are usually found. Coupled with these findings, impairment of motility and slight anemia, with loss of color and vigor, are noted in early carcinoma. The invaluable help of the X-ray should never be neglected and will confirm the clinical and chemical examination, as a rule. The picture is now highly suspicious and no time should be lost in procuring the services of a competent surgeon.

The history may point to an abrupt onset with active progressive symptoms. Such cases run a more rapid course than the more usual form with gradual, insidious onset, and prompt action is necessary, if they are to reach the surgeon in time for successful resection. Here may be pointed out that Friedenwald and Grove contend that there is present in carcinoma of the gastro-intestinal tract a fairly characteristic curve of sugar tolerance, reaching 0.24 percent. or higher within 45 minutes after the ingestion of dextrose and remaining at this level for at least two hours. Palmer (16) states that the "acid test" which is usually positive in cases of gastric and duodenal ulcer has also been found to be positive in certain cases of gastric cancer, usually in those in which free acid is present and in which the free acidity is a factor in the pain.

#### EARLY DIAGNOSIS OF CANCER FORMING ON A PREVIOUS ULCER

The appetite lessens, the other local symptoms, especially the gastric pain, becomes increased and is more con-

stant. Its character may change to a more dull, sickening ache, nausea and vomiting are more frequent; occult blood in the feces is more constant and visible bleedings in small amount in the vomitus. The general features, emaciation and weakness, or the cachexia are soon observed to be greater than is present in gastric ulcer. Again, the gastric analysis yields less characteristic findings than in the usual form of cancer of the stomach, especially in the early stage of the case. The hyperacidity of ulcer may persist. An X-ray examination is imperative.

#### DIFFERENTIAL DIAGNOSIS

The symptoms in the beginning of a case of gastric carcinoma, gastric ulcer, and chronic gastritis are almost identical, and yet it is of the highest importance to know definitely which of the three conditions is present. Painstaking study by employment of modern methods will often detect a localized lesion quite clearly. In such an instance the diagnosis is narrowed to a differential study of ulcer from carcinoma.

The symptoms of chronic gastritis may bear a close resemblance to those presented by the early stage of gastric carcinoma. There is, however, an absence of anemia and emaciation, but no actual localized pain upon pressure in chronic gastritis, merely slight diffuse tenderness. Again, an X-ray examination proves entirely negative, and the contents of the stomach contains free hydrochloric acid, but no lactic or fatty acids after the Boas test meal.

The distinction between gastric carcinoma and gastric ulcer is not always

easily drawn in the incipient or early stages of these affections. It may be noted, however, that cancer occurs in older persons, and unlike ulcer, which is more frequent in females, is more common in males. The pain in gastric carcinoma is but little affected by the ingestion of food and other symptoms of indigestion, especially anorexia, are more marked than in ulcer. The stools give a constant reaction for blood in carcinoma; this is less frequently met with in gastric ulcer. In both ulcer and carcinoma, there may be a palpable mass at the pylorus, but in the former condition, it is only met with in long standing cases, whereas in the latter, it may rarely be detected early.

The temperature in carcinoma of the stomach is usually subnormal, interrupted by intermittent attacks of slight fever, whilst in ulcer the temperature is normal, as a rule. There may be pallor and debility in ulcer, but no cachexia and no peripheral glandular enlargements, which occur in cancer. The absence of free hydrochloric acid is noted in cancer of the stomach, whereas in ulcer there is an excess of hydrochloric acid, as a rule. The duration of cases of ulcer is often exceedingly prolonged, whereas in carcinoma the average duration is less than two years. It must ever be recollected that the X-ray findings should serve to distinguish ulcer from carcinoma of the stomach, even in the earlier stages of these affections, in the great majority of the cases, at least. Unless all of the associated symptoms and signs point collectively to ulcer, an exploratory operation is to be advised.

It is to be recollected that an exploratory investigation can only lead to successful surgical treatment in an early stage of the disease. Rarely, is an exploration done early enough to permit of complete removal of the diseased area of the stomach wall. It might well be asked, is this creditable to the medical profession in view of the fact that extirpation alone offers hope of cure? Cases of gastric cancer first fall under the care of the physician, and should be recognized sufficiently early by him to permit of successful surgical intervention. A really grave responsibility, therefore, rests upon him, and it is a sad commentary upon his diagnostic acumen that only about 15 per cent of the cases reach the surgeon in time to make a satisfactory resection. I feel strongly that it is quite possible to diagnose a much larger percentage sufficiently early to be cured, provided that the physician will start a thorough laboratory investigation into the given case upon the appearance of the earliest suspicious features.

The physician has a definite duty to perform to sufferers from dyspepsia with tendency to persist in persons in late middle life, and in failing to meet this obligation, he is guilty of something more than mere neglect, for we must all agree with Sir Berkley Moyinhan, that surgery has outpaced medicine in the treatment of gastric carcinoma.

Lastly, our inability to cure cancer by medicinal and hygienic measures is a tacit acknowledgment of the insufficiency of the healing art, but since surgery is sometimes effective, if re-

sorted to early enough, the whole profession should concentrate on the study of the disease by the newer scientific methods of diagnosis, with a

view to affording the otherwise doomed patient a chance for life through the only avenue known to science.

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# The Diagnosis of Operable Carcinoma of the Stomach\*

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THE study here reported was undertaken with the object of estimating the relative importance of various criteria in the diagnosis of carcinoma of the stomach. It seemed particularly desirable to assess the value of diagnostic evidence in operable as distinguished from inoperable carcinoma. Our data were obtained from the histories of cases of carcinoma of the stomach diagnosed at the Mayo Clinic from 1920 to 1924 inclusive.

## SELECTION OF CASES

Recurrent cases were excluded. In order that we might have some basis for contrast and comparison, the cases in which operation was not performed were classified according to the reasons for such decision, while those in which operation was performed were grouped according to the operative procedure. It will be seen from Table I that the clinician, the roentgenologist and the patient each contributed to the classification. In rejecting cases the clinician was influenced by external evidence of metas-

tasis which precluded the removal of all malignant tissue, rigid fixation of

Table I

CLASSIFICATION OF CASES 1920-1924	
Operation not performed.....	928
1. Rejected by clinician without roentgen-ray examination ....	110
2. Inoperable by roentgen-ray examination .....	531
3. Operable by roentgen-ray examination; rejected by clinician	90
4. Operability by roentgen-ray examination doubtful; operation not urged .....	128
5. Operable by roentgen-ray examination; patient rejected or delayed operation .....	69
Operation performed .....	1159
6. Exploration only .....	432
7. Palliative gastro-enterostomy..	203
8. Resection .....	524

an epigastric tumor, and in a few instances debility of the patient which rendered the immediate risk of operation prohibitive. In most cases the roentgenologist was responsible for the rejection. By combined fluoroscopic and palpatory examination he demonstrated that the lesion was inaccessible, or that the extent of the infiltration



made resection impossible. In a considerable number of cases, including those in Groups 4 and 5, the patient refused operation. It would be interesting to speculate on the possible reasons for this attitude, but certainly an important one is the opinion of many laymen and certain physicians that carcinoma of the stomach presents a hopeless outlook. The data in Table 1 also show that considerable latitude must be exercised in selecting cases for operation, and this condition must exist until more accurate means are at hand for determining before operation the feasibility of resection, and more especially the presence or absence of internal metastatic lesions and direct extension to contiguous vital structures. On the other hand, unless there is definite evidence that a lesion is not resectable, exploration will always be justifiable if a competent surgeon and surgical facilities are available. There is bound to be an irreducible error of judgment on the part of both clinician and roentgenologist as regards operability.

#### RELATION TO TREATMENT

In the light of our present knowledge of gastric carcinoma surgery provides the only treatment which merits serious consideration. Any appraisal of end-results necessarily involves a clear distinction between the prognosis in all cases of gastric carcinoma and the prognosis in cases of resectable carcinoma. If we direct our attention to the actual results of surgical treatment, we find that the immediate mortality after skillful resection is not formidable, while the percentage of three-year, five-year, and apparently complete cures is gratifying. The assist-

ance of the internist in the preoperative preparation of patients with dehydration, anemia and toxemia of stasis has materially lessened the immediate mortality of operation. For example, Balfour has reported 120 consecutive resections of the stomach for malignant disease with nine deaths. Because gastric carcinoma occurs most frequently late in life it is permissible to calculate the period of survival in terms of the expectancy of life for the age and sex of the individual patient. In this series the average age of patients was fifty-two years for men and fifty years for women. At fifty-two years the life expectancy for men is twenty years. Moreover, if the patient eventually succumbs to carcinoma, the apparent recurrence may be an expression of predisposition to carcinoma rather than failure of surgical treatment. Finally, the morbidity or degree of actual suffering resulting from deprivation of food and water may be materially lessened by palliative resection or gastro-enterostomy. It is a paradox that many patients who reject surgical treatment in the early and probably curable stages of the disease seek eagerly for the welcome palliation which it may afford in the incurable stage. A malignant neoplasm in the pyloric portion of the stomach is accessible to the surgeon and, if the diagnosis is made early, resection with complete removal of the growth is practicable. It has been estimated that in 75 per cent of cases the lesion is situated primarily in the pyloric region. Since resection was possible in only 25 per cent of cases in the series reviewed here, it follows that approximately half of all patients were denied their only

chance of cure or prolongation of life because of late diagnosis. Failure to recognize gastric carcinoma in the operable stage is the most formidable hindrance to successful treatment. In a proportion of cases early diagnosis is precluded by an insidious onset, rapid growth and a fulminating type, but in this series the average duration of symptoms was approximately eleven months; late recognition must therefore be attributed in the majority of cases to tardy or incomplete examination.

#### METASTASIS

The distribution of demonstrable metastatic lesions in our series of patients not operated on is shown in Table 2. Peripheral nodules are frequently demonstrable in several situations in the same patient. In this

Table 2

INCIDENCE AND SITE OF METASTASIS IN 928  
CASES OF CARCINOMA OF THE STOMACH;  
OPERATION NOT PERFORMED

Situation	Definite	Suspicious	Total
Rectal shelf .....	131	24	155
Liver .....	112	21	133
Supraclavicular			
lymph nodes ....	76	11	87
Peritoneum (ascites)	55	6	61
Umbilicus .....	26	3	29
Chest .....	9	17	26
Miscellaneous .....	50	24	74
Total .....	459	106	565

series 565 definite or suspected metastatic tumors were present in 353 cases in a total of 928. Metastasis occurred in 38 per cent. A careful search for metastasis is an important adjunct to the roentgen-ray examination in estimating operability since no matter what the roentgenogram shows com-

plete removal of all malignant tissue will be impossible if distant growths are present. In case of doubt accessible nodes, such as the supraclavicular, may be submitted to biopsy. In the following case the node proved to be tuberculous and satisfactory resection of a pyloric carcinoma was accomplished later.

*Case 1.*—A farmer, aged fifty-one years, registered at the Mayo Clinic August 10, 1919. He had been losing strength and weight for seven months and was easily fatigued. He also noticed belching, especially in the morning. Two months later he began to vomit two or three hours after meals. About this time he noticed a small swelling in the right side of the neck which gradually grew larger. This was followed by a dull "rolling" pain in the middle of the epigastrium, which was relieved by vomiting. The pain and vomiting increased in frequency and severity. He was then awakened at midnight or shortly after by epigastric pain. Vomiting no longer brought complete comfort. The pain was sometimes relieved by soda.

A test-meal did not disclose free hydrochloric acid, and 810 c. c. was recovered. The hemoglobin was 48 per cent, and erythrocytes number 4,040,000. The patient had lost 30 pounds in weight. There were visible peristaltic waves in the epigastrium, with a palpable ridge-like tumor lying transversely. The cervical lymph nodes on the right were hard. The roentgenologic report was operable carcinoma of the stomach.

August 23, 1919, a node excised from the right side of the neck was found to be tuberculous. September 14, 1919, partial gastrectomy was performed for carcinoma of the pyloric end of the stomach. The tumor measured 9 by 9 by 2 cm. There was moderate lymphatic involvement and extensive involvement of the serosa.

The age and sex incidence in cases of gastric carcinoma and other surgical causes of dyspepsia are compared in

Figure 1. Although the average age of incidence in cases of carcinoma is higher than in the others, the fact is of little real value in differential diagnosis. On the contrary, the term "cancer age" is relative rather than absolute and may be misleading unless its qualifications are appreciated. The age and sex of a patient may create a suspicion as to the cause of the dys-

time-worn criteria for diagnosis: retention, achlorhydria, palpable tumor, loss of weight, and anemia. Even acknowledging that each of these signs is of value when present singly or in various combinations, one must at the same time be prepared to suspect and recognize operable carcinoma in the absence of most or even all of the signs (Table 3).

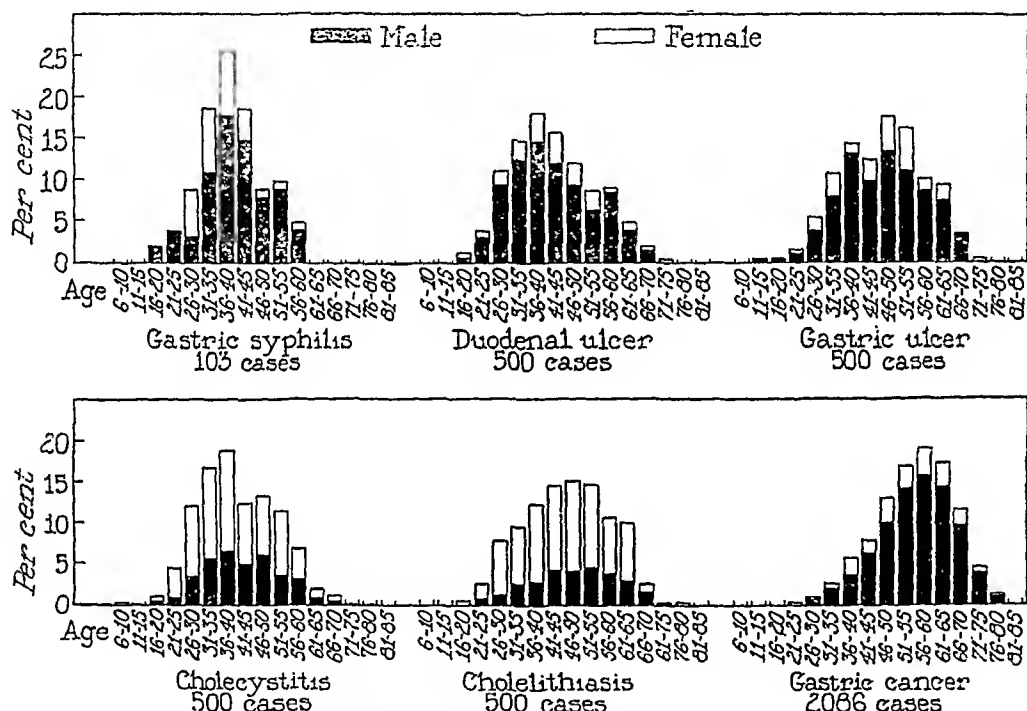


FIG. 2. Anemia in cases of organic dyspepsia.

pepsia, but should not in any sense be relied on for diagnosis. It is at least true that carcinoma of the stomach may be encountered during any age period after twenty years.

#### VALIDITY OF OLD CRITERIA

Any evidence which may create a justifiable suspicion of carcinoma or have positive value in influencing a decision in an individual case must not be ignored. It is equally important for one to admit the shortcomings of the

*Retention.*—Gross retention\* is not in itself an unfavorable sign since it suggests that the gastric wall above the obstructing tumor is dilatable and,

\*The term retention is used to indicate interference with motor function.

The degree of interference may be measured in various ways and for the purposes of this study an arbitrary standard was selected as follows: Early in the morning patients were given a test-meal consisting of 40 gm. of carbohydrate food (arrow root biscuits) and 400 c. c. of water. This meal was given without emptying the stomach of

Table 3  
SYMPTOMS AND SIGNS

	Cases	Test-meal		Free hydrochloric acid		Retention		Tumor		Hemoglobin, per cent (Average)		Loss of weight, pounds (Average)		Duration of symptoms (Average)	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Males	Females	Males	Females	Months	
Considered inoperable by clinician without roentgen-ray examination .....	110	15	13.6	2	13.3	10	66.6	91	82.7	58	56	31	41	9.7	
Inoperable by roentgen-ray examination .....	531	342	64.4	50	14.6	54	15.5	338	63.7	61	62	29	32	11.7	
Operable by roentgen-ray examination; rejected by clinician ....	90	60	66.6	20	33.3	26	29.0	66	73.3	60	58	25	33	8.5	
Operability by roentgen-ray examination doubtful; operation not urged ....	128	85	66.4	14	16.4	31	24.2	91	71.1	60	60	24	33	10.3	
Operable by roentgen-ray examination; patient rejected or delayed operation.	69	56	81.1	18	32.1	28	40.5	36	52.1	62	61	24	28	9.7	
Exploration only..	432	351	81.2	124	35.3	137	31.7	288	66.6	65	66	24	29	8.2	
Palliative gastroenterostomy ....	203	140	68.9	81	57.8	124	61.0	122	60.1	61	60	29	31	8.9	
Resection .....	524	477	85.3	239	53.4	240	46.0	259	49.4	67	65	23	24	10.9	

fasting contents, or of any contents remaining over-night. Aspirations were commenced one hour afterward. If free acid was found in the first aspiration the stomach was emptied. If free acid was not found, fractional aspirations were made every fifteen minutes for an hour. At the time of the fourth aspiration, one and three-quarters hours after the test-meal was given, the stomach was emptied. Certain exceptions were made to this rule, as when gross food particles from previous meals were obtained. In such instances the stomach was emptied by using a large stomach tube. It is found in practice

that when this technic is used the total content normally recovered is usually between 100 and 150 c. c. The term retention is used here when the recovered content measured 150 c. c. or more. In fact where retention is recorded the recovered content was usually grossly in excess of this amount. We do not believe that evidence of slight degrees of motor dysfunction, for example an amount of 160 c. c., has diagnostic significance since such an amount may be encountered in such conditions as migraine. In some cases of gastric carcinoma the emptying time is rapid, the amount recovered being less than 100 c. c.

therefore, presumably not infiltrated by the neoplasm. If there is a good deal of healthy wall, resection is more likely to be feasible. Our study, however, shows that gross retention was encountered most often in association with pyloric lesions which, because of local extension to contiguous structures, were not resectable. The advantage accruing from failure of the growth to infiltrate the gastric wall widely was offset by its penetration to organs extrinsic to the stomach.

*Anacidity.*—In more than half of all cases resectable carcinoma can be recognized when free hydrochloric acid is present in the aspirated gastric contents. The presence of free acid, therefore, is not a good reason for rejecting the possibility of carcinoma. Attempts have been made to utilize, in diagnosis, curves constructed from fractional aspirations, but so far the published results do not convince one that the fractional method furnishes dependable data on which to differentiate intragastric lesions, or that it possesses any advantage over the single aspiration for this purpose. Anacidity and retention are important supplementary factors in diagnosis. The demonstration of gross retention by the use of the stomach tube points to the necessity for a short period of preoperative preparation to lessen the associated gastritis, to restore muscle tone, and to combat dehydration. The routine test-meal is, therefore, desirable not only to demonstrate anacidity but to secure objective evidence in support of motor dysfunction. If the history reveals recent hematemesis or the patient is extremely weak, the stomach tube should not be used.

Table 3 shows that in 14.7 per cent of the cases in this series that proved to be resectable a test-meal was not considered necessary.

*Palpable tumor.*—The incidence of palpable tumor is less in resectable than in nonresectable cases. Table 3 shows, however, that a diagnosis may be made in the most advanced cases without palpable tumor, and that the presence of a tumor does not preclude successful resection. Fixation of a tumor which is confined to the left side of the epigastrium usually, but not invariably, indicates that it is inoperable. The roentgenologist's opinion that the lesion is inoperable should support a decision to reject a case for operation. In rare cases this opinion may be overruled, as when a patient is in good condition to withstand an operation and the tumor is mobile to some extent. Successful resection when roentgenologic evidence pointed to inoperability is illustrated by the following case.

*Case 2.*—A section foreman, aged fifty-three years, registered September 18, 1920. Nine months previously he had noted a sense of soreness in the epigastrium with distention, flatulence, belching, and sour eructations coming on soon after eating and passing away after three or four hours. There had been distress daily since the onset, with increasing discomfort for a month. Sour foods or fruits aggravated the discomfort and the patient was afraid to eat. He had lost 15 pounds in weight.

A fractional test-meal showed anacidity in four fractions. The hemoglobin was 61 per cent, and erythrocytes numbered 3,850,000. There was an irregular, hard, movable mass in the left side of the epigastrium. The roentgenogram showed inoperable carcinoma of the stomach with retention. October 6, 1920 three-fourths of the stomach was re-

sected. The carcinomatous mass measured 11 by 11 by 3 cm. and extended through to the serosa. Lymphatic involvement was not found. February 28, 1927, the patient reported that he was working every day and that his weight was normal.

Free mobility of a tumor in any situation is a favorable sign, although a pyloric tumor may infiltrate adjacent structures through an attachment which permits relatively free movement; such infiltration may preclude resection. From a diagnostic viewpoint the important fact is that gastric carcinoma may exist without palpable tumor. On the other hand, when a palpable epigastric mass is associated with roentgenologic evidence of an intragastric lesion the probability of malignancy is overwhelming. Rare exceptions are encountered, as when a perforating benign ulcer gives rise to a tender inflammatory mass. A still more rare exception is met with in cases of large benign neoplasm. In a case recently observed an intragastric hair-ball gave rise to a large mobile tumor.

*Loss of weight.*—The actual and relative loss of weight in cases of gastric carcinoma is greater in women than in men. We are unable to demonstrate a consistent relationship between loss of weight and any other single factor, such as anemia, retention, or anacidity. Rapid loss of weight is an unfavorable sign. On the other hand, with an extensive lesion there may not be loss of weight, so maintenance of body weight does not justify exclusion of carcinoma as a possible explanation of persistent dyspepsia. In the following case palpable tumor, anemia, or loss of weight was not present.

*Case 3.*—A laborer, aged forty-six years, registered January 9, 1924. For fifteen years he had suffered from spells of stomach trouble which lasted from two or three hours to two or three days; at first, intervals of from two weeks to three months occurred between spells, but gradually they lessened and the spells lasted longer. The distress came on at once after eating, as a dull, heavy feeling in the epigastrium, succeeded by vomiting. Usually the vomitus contained some food eaten the previous day. Severe occipital headache occurred and sometimes the attacks were followed by numbness in the fingers and lips. Weight had not been lost.

A fractional test-meal showed free hydrochloric acid 0, 0, 10, and 12. The hemoglobin was 74 per cent, and erythrocytes numbered 4,560,000. A tumor was not palpable. The roentgenograms showed an operable lesion in the posterior wall of the stomach, probably malignant. December 13, 1924, segmental resection of the stomach was performed. The carcinoma measured 3.5 by 3.5 by 1 cm. The lymphatics were not involved. The carcinoma had apparently developed on a polyp.

It seems probable that the loss of weight in cases of gastric carcinoma is proportional to the decreased intake of food. Decreased intake is not always due to lack of appetite, but often results from fear that food may cause distress.

*Anemia.*—Text-book tradition teaches that anemia in gastric carcinoma may be caused by toxins elaborated by the neoplasm. We are not aware of any proof to the contrary, but are convinced that gross or occult hemorrhage affords a better explanation. Moreover, marked anemia is relatively rare in cases of resectable carcinoma. Figure 2 shows that in 47 per cent of cases of resectable carcinoma the hemoglobin readings fell within normal limits and severe anemia

(less than 50 per cent hemoglobin) was present in only 17 per cent of cases.\*

At the Mayo Clinic the stools have not been examined for occult blood as a routine in cases of suspected gastric carcinoma. We cannot, therefore, from experience assess the relative

When the roentgenologist fails to discover an intragastric lesion in a case of suspected gastric carcinoma evidence of gross organic disease in the upper part of the abdomen will often be sufficient to warrant exploration. If such evidence does not exist, a meat-free diet is prescribed, and the stools

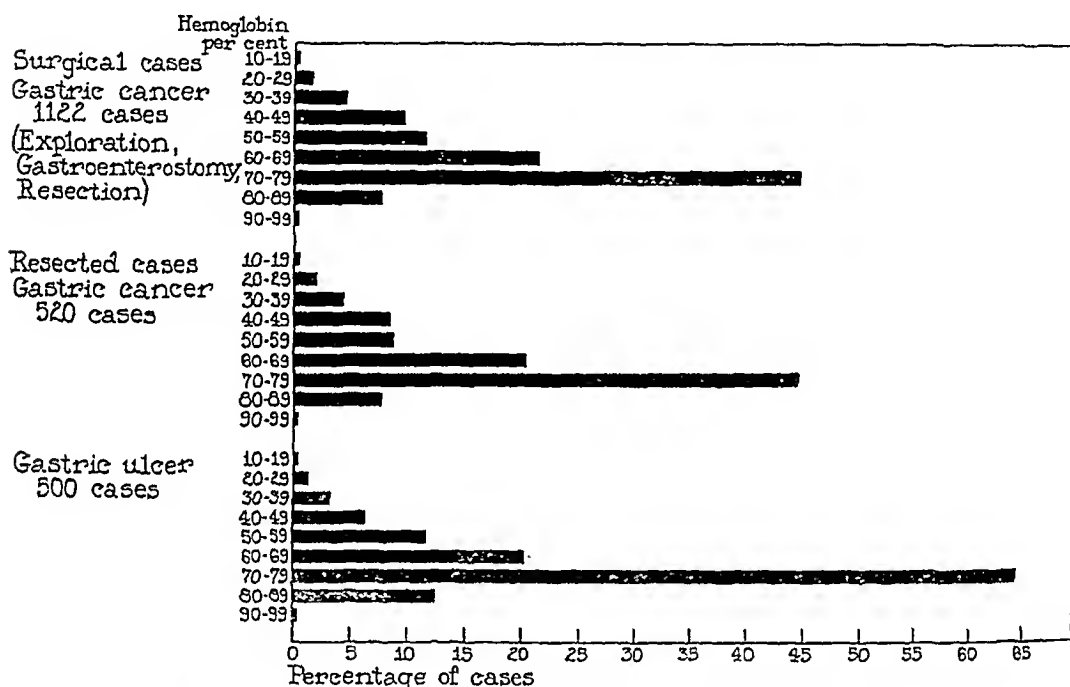


FIG. 1. Age and sex incidence in cases of organic dyspepsia.

diagnostic value of finding occult blood. We believe, however, that the time necessary to carry out this test can be spent to the patient's advantage in more precise diagnostic procedures, especially roentgenologic examination.

\*The hemoglobin readings given are those obtained by instruments used as a routine in the clinical laboratories. It has been shown by study that the results obtained with these instruments compare favorably with those from more exact methods when hemoglobin percentages are below 75 per cent; above this range these instruments in our hands fail to show satisfactory graduations. Thus, an average hemoglobin reading in 100 presumably normal subjects was 75 per cent.

are examined for occult blood. If blood is found there is no certainty that it comes from the stomach, or that if it does its source is carcinoma. On the other hand, if blood is not found, carcinoma is not definitely excluded. Gastric carcinoma cannot be precisely diagnosed in any case on the unsupported evidence of occult blood. Supplementary evidence must be furnished, such as the history of dyspepsia, anacidity, or loss of weight and strength, and other sources of bleeding must be excluded. If this supplementary evidence is considered apart from the finding of occult blood, there will

usually not be any question of the advisability of exploration. In any case it has seemed to us that search for occult blood can be conveniently reserved for obscure cases in which the clinical history and physical and roentgenologic examinations are inconclusive.

#### RELATIVE VALUE OF DIAGNOSTIC AIDS

*History.*—The history with regard to the onset, course, and character of the dyspepsia may be important in diagnosis but we hesitate to assign it any definite rank or order of precedence because, in our experience, the dyspepsia associated with resectable carcinoma is much more variable, and much more likely to simulate that of other surgical or functional types of dyspepsia than is generally taught. The dyspepsia of carcinoma may descend upon a patient out of a clear sky and run a uniformly persistent and rapidly progressive course. Such an onset is likely to alarm the patient and his physician, and although the diagnosis may be made early in such cases in point of time the fulminating course may have carried the local lesion beyond the point of resectability.

The anatomic situation of a lesion is perhaps of first importance in the production of discomfort. A lesion situated at either orifice of the stomach will produce motor disharmony earlier than one in the body, and in the latter situation it will be earlier manifest if in the so-called gastric canal than if on the greater curvature or posterior wall. As has been intimated, it is a serious mistake to assume that the dyspepsia of carcinoma invariably manifests itself either by a sudden onset or a persistent course. Antecedent or-

ganic or functional dyspepsia does not protect a patient against carcinoma. Thus, the patient known to harbor a diseased gallbladder or appendix, or who is under treatment for anacidity, migraine or peptic ulcer, or who belongs to the group of the constitutionally inferior, whose digestion breaks down under mental or physical strain, is just as deserving of suspicion of carcinoma as the previously healthy patient. Many of the tragedies of gastric carcinoma are directly due to a false sense of security engendered in the mind of the patient or his physician by the presence of chronic dyspepsia. Whether the dyspepsia of carcinoma may in some instances be said to simulate the dyspepsia of peptic ulcer depends on the observer's opinion of what constitutes a peptic-ulcer history. In our experience it is not unusual for a patient with carcinoma to state that epigastric distress comes on two or three hours after the taking of food, that such distress is relieved by soda or by more food, and that he has been free from distress for weeks or months at a time. It might be assumed that such a history would be confined to cases of carcinomatous ulcer, but our study showed that fungating lesions are often characterized by what may be termed an ulcer course. On the other hand, some patients with carcinomatous ulcer fail to show periodicity in the daily sequence of discomfort characteristic of ulcer. In rare instances a benign ulcer may be found in association with a malignant ulcer, as illustrated by the following case.

*Case 4.*—A bank clerk, aged forty-eight years, registered December 29, 1918. For fifteen years he had suffered from intermit-



tent stomach trouble. Pain occurring when the stomach was empty had been relieved by food and soda. At first the attacks did not occur often. For about a month before admission the pain would come on from two to four hours after a meal; it had also awakened him at night. Food or soda still brought relief. The pain was situated in the right side of the epigastrium and at the tip of the scapula. Two weeks prior to examination vomiting had occurred twice, the vomitus being brownish fluid with coffee-ground sediment. Four weeks before admission there had been an attack of severe pain in the left flank which radiated to the left groin; the abdominal wall became board-like, and morphin was administered. He had lost 6 pounds in weight. At the time of examination there was still a little soreness in the left flank. Tumor was not palpable. A test-meal showed total acidity 68 and free hydrochloric acid 32; 100 c. c. was recovered. Hemoglobin was 75 per cent, and erythrocytes numbered 4,920,000. Roentgen-ray examination showed a large ulcer on the lesser curvature of the stomach. Partial gastrectomy was performed January 7, 1920. A carcinomatous ulcer 2 by 2 cm. was found, commencing 2 cm. from the pylorus on the lesser curvature; there was moderate lymphatic involvement. There was also a benign ulcer 3 cm. in diameter above the carcinomatous ulcer on the lesser curvature.

In an attempt to learn what might reasonably be assumed to be the earliest symptoms or signs of carcinoma, a review was made of the histories of a group of cases with resectable lesions in which the total duration of symptoms was less than two months. These were compared with the first symptoms and signs in cases dating back two years. Strangely enough there was not any appreciable difference in the two groups. In a few cases an epigastric tumor was the first sign noticed. In most cases pain was the premonitory symptom. Vomiting, hematemesis,

and loss of strength and weight followed in order. Cases with an insidious onset of ill health without signs or symptoms referable to the stomach constitute a small but important group which should be differentiated from chronic nephritis and the malignant blood dyscrasias. In most cases there were definite symptoms. What was really lacking was an appreciation of the possible significance of these early manifestations.

*Roentgenologic data.*—Various authors writing on the diagnosis of carcinoma of the stomach complain of the growing tendency to depend on the roentgenogram. They suggest either by inference or direct statement that the roentgenologic examination is inferior to other clinical methods of diagnosis, and point out that the history, physical examination, test-meal, and stool examination, may serve to establish a diagnosis in cases missed by the roentgenologist. The fear that clinical acuity may be lessened by reliance on precise mechanical methods of diagnosis may be, and often is, unduly stressed, while the gain to the clinician through the use of such means is overlooked. It is true that the value of roentgenology depends on its thoroughness, and on the examiner's skill, keenness of observation, experience and judgment. The roentgenologist may overlook or misinterpret. In Table 4 are compared the roentgenologic evidence of an intragastric lesion in cases in which operation was performed with other data usually considered of value in diagnosis. It will be seen that the chance of demonstrating a lesion by roentgenologic examination is overwhelmingly greater than

the chance of finding a palpable tumor, anacidity, retention, or anemia. The mere portrayal of a lesion is an important step in the elucidation of the character of any type of dyspepsia. The

tation. It is also important to bear in mind that in the cases in which roentgenologic interpretation is difficult the supplementary manifestations are more likely to be absent.

Table 4  
INCIDENCE OF OBJECTIVE DIAGNOSTIC DATA

	Exploration only, per cent.	Palliative gastro- enterostomy only, per cent.	Resection, per cent.
Roentgen-ray evidence of lesion .....	98.8	100.0	98.2
Tumor palpable .....	66.6	60.1	49.4
Anacidity .....	64.7	42.2	46.7
Retention (more than 150 c.c.) .....	31.7	61.0	46.0
Anemia (hemoglobin less than 60 per cent) .....	27.7	39.2	24.0

Table 5  
ROENTGEN-RAY DATA IN CASES IN WHICH OPERATION WAS PERFORMED

	Exploration only	Palliative gastro- enterostomy	Resection
Gastric ulcer; no reference to carcinoma .....	19	18	46*
Gastric ulcer, probably malignant .....	3	..	1
Carcinoma, inoperable .....	124	13	58
Carcinoma, operable, operability doubtful, or operability not mentioned .....	206	112	285
Lesion .....	42	32	92
Duodenal ulcer .....	1	3	7
Miscellaneous .....	15	4	9
Negative .....	5	..	9
Roentgen-ray examination not made .....	17	21	17
Total .....	432	203	524

\*In these cases in which the roentgen-ray appearance was that of ulcer the lesion proved to be a carcinomatous ulcer in twenty cases, and a diagnosis was only possible after microscopic examination in seven of these.

interpretation of the character of the lesion is more difficult and the chances of misinterpretation are greater in resectable than in inoperable carcinoma, but it must not be forgotten that other evidence as well as the roentgenologic must be submitted to judicial interpre-

The roentgenologist's interpretation in the cases of gastric carcinoma in which operation was undertaken is summarized in Table 5. In fifty-five cases out of a total of 1159, the operation was not preceded by roentgenologic examination. In two of these

cases exploration was undertaken for the relief of undifferentiated ascites. In the remaining fifty-three cases the clinical diagnosis was carcinoma of the stomach. In fourteen cases out of 1104 examined (1.3 per cent) operation was advised in spite of a negative roentgenologic examination. In the series of cases of resectable carcinoma, the roentgenologist, although he found an intragastric lesion, was unable to say that it was malignant in 154 of 507 (30 per cent) examined. This seems to be extremely important. To appreciate it fully let us keep in mind that the roentgenologist at least discovered a lesion in these cases. It seems a crucial fact that in the discovery of operable carcinoma, as exemplified by this series, it is necessary to advise exploration in a considerable number of cases in which it is impossible to be sure before operation whether or not the lesion is malignant.

In Table 5 it will be seen that a roentgenologic diagnosis of gastric ulcer was made in forty-six instances in a total of 507 cases which at operation proved to be carcinoma. Pathologically the resected specimens were reported as carcinomatous ulcer in twenty, and as nonulcerating carcinoma in twenty-six. In the group of carcinomatous ulcer the diagnosis of malignancy was possible from the gross appearance in thirteen, while in seven malignancy was detected only after microscopic examination. In one instance, in which the diagnosis was made only after microscopic examination, the patient eventually died from recurrent carcinoma of the stomach.

In the resected specimens, in these

forty-six cases interpreted roentgenologically as gastric ulcer, benign ulcers were found in association with malignant disease in five instances. The association was as follows: carcinomatous ulcer and two benign ulcers in one case; nonulcerating carcinoma and three benign ulcers in one case; carcinomatous ulcer and one benign ulcer in two cases, and carcinoma and one benign ulcer in one case. The occasional association of benign and malignant lesions suggests that a remote history of dyspepsia simulating that of benign ulcer may in a few instances be due to the nonmalignant lesion, while the recent progressive distress may be attributable to the occurrence of carcinoma. It may also explain the roentgenologic reports in a few instances, but a review of the data shows that in twenty-four instances in a series of forty-six cases a nonulcerating carcinoma simulated roentgenologically a benign ulcer. In many of these cases there were suggestive points in the history or in the other laboratory data. If an acidity is present the presumption is warranted that the intragastric lesion seen by the roentgenologist is carcinoma, but it cannot be too strongly emphasized that when the roentgenologist is in doubt the clinician will usually not have information of superior diagnostic worth. In dealing with an undifferentiated intragastric lesion no apology need be offered for advising exploration. If we wait for certain diagnosis we may wait until cure is impossible. If the patient is not to be denied the possible benefits of skillful surgery, carcinoma must be excluded not only as a probability but also as a possibility.

# DIFFERENTIAL DIAGNOSIS

Assuming that the patient presents himself for examination and that such examination is comprehensive and thorough, there will seldom be any real difficulty in deciding on appropriate treatment even though accurate differentiation is not always possible. By far the most important step is to determine whether there are roentgenologic signs of an intragastric lesion. An intragastric lesion may be carcinoma, syphilis, benign tumor, simple benign ulcer, or benign ulcer complicated by perforation or perigastric adhesions.

*Syphilis.*—When the Wassermann reaction of the blood is positive, roentgenologic evidence of an intragastric lesion is more likely to indicate carcinoma than gastric syphilis. That is to say that the incidence of gastric carcinoma in cases of syphilis is greater than the incidence of gross structural change in the stomach due to syphilis. Gastric syphilis occurs in two forms. Usually it infiltrates the walls extensively and produces a dumb-bell shaped deformity, the orifices being free. The symptoms in such cases are characteristically attributable to restriction of the gastric capacity. It is sufficient for our purposes here to say that such cases would be inoperable if they were due to carcinoma, and antisypilitic treatment may be instituted without prejudice. In the second form, in which a syphilitic lesion, usually a serpiginous ulcer, sometimes a gumma, is confined to the pyloric end of the stomach, differentiation is not easy. A therapeutic test may permit a malignant lesion to grow into the stage of inoperability and it

would seem safer as a rule to advise resection of such a tumor.

*Benign tumor.*—Benign tumors should be resected in any case, and the only point of interest in attempting differentiation is that a benign tumor situated in the upper third of the stomach may be resectable because its attachment to the gastric wall may be relatively small, whereas a malignant tumor in the same situation would be inoperable because it had infiltrated widely.

*Benign ulcer.*—The differentiation of benign ulcer and malignant neoplasm is of greater interest because the problem of differentiation will arise more often. It is perhaps desirable to state here that in diagnosis we are not concerned with the academic question of whether benign ulcer degenerates into carcinoma. We are confronted with certain more pertinent facts which, briefly stated, are as follows:

A certain number of cases of carcinoma of the stomach present at the onset and throughout the resectable stage a syndrome so closely paralleling peptic ulcer that differentiation by history or test-meal is impossible. In our series of resectable carcinoma (Table 5), the roentgenologic appearance of the carcinoma was interpreted by experienced roentgenologists as indicating benign ulcer in fifty-three out of 507 cases examined (10 per cent). A complicated benign lesion may simulate a malignant lesion roentgenologically. These facts are set down in the full consciousness that benign gastric ulcer is a definite pathologic entity remaining as a rule, if not always, benign throughout its life history, healing

spontaneously sometimes, producing periodic disability usually, and often becoming complicated by chronic perforation with subsequent deformity from cicatrix or adhesions. If a patient presents himself with a history of several years' standing characteristic of peptic ulcer, if there has not been any change in the degree of discomfort nor in the rhythmic periodicity of attacks, if free acidity is high, and if the roentgenologic examination reveals a small ulcer, it may be concluded with some assurance that the lesion is benign, but it must be borne in mind that there are not any symptoms of benign ulcer of the stomach which may not be simulated singly or in any combination by malignant ulcer. On the other hand, one may frequently feel reasonably sure that a gastric ulcer is malignant, especially if the onset is late in life, if the history is short, if anacidity or hypo-acidity is present, if the symptoms are irregular, and if the roentgen-ray reveals a large lesion. It has been frequently suggested that, when there is any doubt, favorable response to a strict medical regimen for ulcer will indicate that the lesion is not malignant. In our opinion this suggestion is open to stringent objections. First, in many cases of carcinoma of the stomach symptoms have disappeared for weeks or months following such a regimen. This has been true not only in certain cases of carcinomatous ulcer, but also in a few cases of well-localized fungating growth. Second, failure to respond may mean that a benign lesion is complicated by perforation or perigastric adhesions. Finally, it cannot be too strongly emphasized that gastric carcinoma never

sleeps, no matter how silent it may be, and a period of such regimen may permit a resectable lesion to become inoperable. It is surely safer to advise surgical exploration when in doubt, since skillful surgical treatment of benign ulcer is followed by excellent results. A common mistake, contributing to the late diagnosis of gastric carcinoma, is to assume that the early dyspepsia of carcinoma is due to benign peptic ulcer. The following case illustrates an "ulcer history":

*Case 5.*—A man, aged sixty years, registered January 19, 1920. A stone had been removed from the bladder by suprapubic cystostomy June 30, 1916. In March, 1917, a gnawing pain began in the epigastrium just above the umbilicus; it commenced two hours after meals and was relieved by food. Soda was not tried. Hematemesis had not occurred. About a year before admission there had been bright red blood in the stools. The distress was persistent except for two periods of remission, each of about six weeks' duration. He had vomited several times in June, 1919, and about five weeks before examination he had vomited a large quantity of sour material. Gastric lavage gave relief. At times the pain was severe at the right costal margin. Under treatment consisting of a milk diet, supplemented with alkalies and rest in bed, he had improved. When the diet was later increased to include custard and cereal he stated that he had very little pain. There had been a loss of 14 pounds in weight.

A tumor was not palpable. Following a test-meal, 625 c. c. of gastric contents was recovered which had a coffee-ground residue, total acidity 68, and free hydrochloric acid 54. Hemoglobin was 81 per cent and erythrocytes numbered 4,800,000. Roentgen-ray examination showed a lesion at the pyloric end of the stomach producing obstruction. Operation, January 27, 1920, revealed a carcinomatous ulcer situated on the lesser curvature of the stomach and perforating onto the anterior surface of the pan-

creas. Three-fifths of the stomach was resected. The pathologic report was: carcinoma 4 by 4 cm. involving the serosa; slight lymphatic involvement.

In the following case of carcinoma of the stomach the roentgenologic signs simulated those found in duodenal ulcer.

*Case 6.*—A housewife, aged forty-seven years, registered September 27, 1920. Three years previously she began to have periodic spells of bloating, belching, and eructation of sour, bitter material, which were relieved by induced vomiting and indigestion of soda; these symptoms were usually worse three hours after meals. There was no actual pain. The spells would last for four or five days and would usually occur during the menstrual period. During the six months before registration the same symptoms recurred almost every day. The patient felt worse at about 4 p. m. Soda still relieved the symptoms, and the next meal would help somewhat in relieving the symptoms. Induced vomiting still gave some relief. Acid foods and fruits made the distress worse. No dietary or medical regimen had been prescribed. There was a loss of weight of 40 pounds.

There was a right inguinal hernia, and a small mobile tumor in the epigastrium. A test-meal showed total acidity 44 and free hydrochloric acid 24; 450 c. c. of rancid, sour material was recovered. The hemoglobin was 55 per cent, and erythrocytes numbered 4,140,000. Roentgen-ray examination of the stomach revealed a deformity which was thought to be a duodenal ulcer causing marked retention. Partial gastrectomy was performed October 8, 1920; the carcinoma was 5 cm. in diameter and was situated at the pyloric end of the stomach. Lymphatic involvement was not found. March 3, 1927, the patient reported a gain of 50 pounds in weight and stated that she was in good health although she was suffering some discomfort from the inguinal hernia.

#### PROSPECT OF IMPROVEMENT IN DIAGNOSIS

It is interesting to note that the average duration of symptoms in the cases of the group of resectable carcinoma was ten and nine-tenths months. A possible reason for the neglect of symptoms may be deduced from the age and sex distribution. While carcinoma of the stomach occurs over a much wider range of years than the average age might suggest, it is nevertheless true that it begins for the most part during an age period in which discomforts due to involutionary degeneration, focal infection, and so forth, are not only to be expected, but are habitually ignored by the breadwinner who must maintain his place in the competitive struggle for existence.

When, then, are the hindrances to the recognition and treatment of resectable carcinoma of the stomach? The disease may be insidious, and the patient may be unaware of any marked discomfort until the lesion is inoperable. We believe, however, that this possibility is exaggerated in the literature. The patient may have a dread of cancer and conceal his distress until it becomes aggravated. The physician may lack the facilities or training to make a comprehensive examination. The well-equipped physician may misinterpret his observations. With the diagnosis either reasonably established or in doubt, the patient may reject or delay surgical treatment. If gastric carcinoma is to be successfully treated the physician must be constantly suspicious or aware of its possible presence, and to this he must add promptness and thoroughness in examination,

and forceful frankness in urging surgical measures.

In our opinion roentgenology holds first place in the diagnosis of resectable carcinoma of the stomach. By means of the roentgenogram earlier and more useful evidence may be secured than by any or all other means. The roentgenologist's interpretation of this evidence must often be supplemented, or amended, by the clinician. The responsibility for early diagnosis

and advice as to appropriate treatment must be shared by the roentgenologist, physician, and surgeon.

For improvement in the present unfavorable outlook in gastric carcinoma as a whole the public and the profession alike must depend to an increasing extent not so much on the surgeon as on the physician, who has earlier access to the patient and an earlier opportunity to make an examination.

# An Unusual Management of Essential Hypertension\*

NICHOLAS LUKIN, M.D., *New York*  
*Report of a Case*

**A**BOUT eight years ago a physician became aware that his customary task of attending to a considerable general practice was gradually growing unbearable. He was about forty-eight years old, five feet eleven inches tall and weighed about two hundred pounds.

Leading a very active life since boyhood he had no complaints or illness for the past twenty years. But, when this history began, he had frequent headaches, dizziness, dyspnoea when hurrying or going up two flights of stairs, became easily fatigued, had casual nosebleeds, suffered from heartburn and other digestive disturbances, was very irritable and felt generally unfit for further work. The pallor in his face and his worn expression were objects of comment by his friends and patients. He then consulted several colleagues with the result that a definite diagnosis of primary or essential hypertension with chronic left ventricular decompensation was made. The presence of a beginning arteriosclerosis was also surmised.

During that time he had applied for a small insurance policy and because

the blood pressure on several examinations proved to be over two hundred systolic, and slightly over ninety diastolic, the policy was refused. On many blood pressure takings since then it remains persistently and uniformly one hundred ninety systolic and ninety diastolic.

He was advised to abandon his work as a general practitioner because in his case the etiological factor of the hypertension were considered to be mental strain, worry and overwork with insufficient rest. The physical strain of stair climbing and attendance to his obstetric practice were deemed the direct causes of his gradual breakdown.

Tobacco was entirely interdicted because he was an incessant smoker of cigars and cigarettes.

A rest cure was also suggested, even absolute rest in bed for a few weeks, in order to lower the blood pressure.

Diet restrictions came next in order. Animal proteins were reduced to a minimum, and caloric intake lessened. Large amounts of all sorts of vegetables were substituted for meat.

Active elimination was strongly urged. Frequent evacuations of the bowels were to be secured daily by salines and vegetable cathartics. Skin

\*Presented before the North Bronx Medical Society, March 10th, 1927.



activity was to be stimulated by sweating. Electric light bath with free ingestion of water during the bath a few times a week were to be very beneficial. Hot packs or daily hot baths were considered next to electric light bath as a substitute.

Restriction of sodium chloride was of course included in the management of case.

The use of coffee was to be given up because of increased irritability.

Unfortunately or rather fortunately he could not follow the regimen thus laid down verbatim.

He was not in a position to give up his practice nor take a rest cure or even rest in bed for a few weeks. His onerous work was only partly reduced. The dietary restrictions, though, he was obliged to comply with because his wife strictly obeyed the doctor's orders and she did the cooking and serving.

Sweating and hot baths were tried casually, but because of frequent "colds" he gave them up. On smoking he compromised by giving up cigars and using only a limited number of cigarettes a day. Drinking of coffee was continued, but in diluted form and diminished amounts.

Ingestion of cold water, even in moderate quantities, resulted in heartburn and was entirely abandoned.

This modified regimen was maintained for several months. But instead of improvement, his condition seemed worse; more dyspnoea, headaches of longer duration, even intermittent claudication appeared occasionally and, in addition, abdominal cramps and dull pains were a frequent occurrence.

He therefore became more worried

and finally decided to apply himself to the subject of hypertension and its sequelae more deeply and see what he can learn in order to help himself. At the same time he prepared himself for a specialty. Thus the burden of his work was increased by added reading and several post-graduate courses in metabolism, cardiography and X-ray.

As a result of special reading on the subject for which he tried to find a check, since a cure was out of the question, the following plan of management was adopted for himself, as well as for his patients in a similar plight.

(1) Work is only restricted to the limits of economic need and psychic satisfaction. All irritating factors surrounding such work or occupation are to be eliminated. Of course, physical overstrain is guarded against. His patients are not told to give up their usual vocations.

(2) Home folks and family are instructed never to assume a negative attitude toward him in conversation or action.

(3) A bulky vegetable diet is strictly eliminated. Those containing a great amount of cellulose, leaving a large residue in the intestines, are forbidden. Only a very small amount of raw and fresh vegetables are allowed as a relish. Legumes, because of the gaseous fermentation which they cause, are also excluded.

(4) A high animal protein diet within caloric needs is adopted. Meat, red or white, twice or even three times a day, well cooked, broiled or roasted, is the dominant food.

(5) To counteract its metabolites with their speculative bad effects, the use of liberal amounts of acid fruits is urged.

(6) While the washing out the natural content of salt from foods is not advised, the addition of salt and the use of very salty dishes is interdicted. Other condiments are permitted.

(7) Coffee in fairly concentrated form is strongly urged to be used instead of water or all other kinds of fluids.

(8) The intake of fats and lipoids are restricted to an unavoidable minimum.

(9) Bread is limited to a minimum and eaten only in the form of dry toast. As it is commonly eaten, though essential in the diet of normals, it is a cause of stasis, hyperacidity, and putrefaction in those affected with cardiovascular disorders.

(10) Sweating, hot and full body baths are forbidden. Cleanliness is maintained by luke-warm showers or hip baths.

(11) Cold showers over head, neck and face every morning are urged.

Other directions which accompany this plan of management of essential hypertension do not differ from those in common use as to rest, amusement and exercise.

The physician who is the subject of this report has benefited by this regimen a good deal and stands presently before you. He is doing more mental and physical work than before and his blood pressure is still one-hundred-ninety systolic and one-hundred diastolic.

He fully realizes that one case is scarcely adequate to change a time hallowed custom of starvation, sweating and purgation in cases of hypertension; nor do the few cases which have been treated in like manner with relatively favorable results enhance the criterion. But the motivation which led into this plan rests on data which seem to deserve a sympathetic consideration and a favorable generalization.

Thus the most outstanding departure from older methods in this plan of treatment is the high protein diet. When first adopted it was to replace the vegetarian foods which gave abdominal discomforts, pain and increased dyspnoea. It was realized that the large fermenting residues left by vegetables were to blame for the increased intra-abdominal tension, intestinal spasm and an added load upon cardiac reserve through pressure on the splanchnic vessels. Meat was chosen to replace them with remarkable relief. The possible harm of its metabolites naturally caused worry, and fruits were used for their "buffer" qualities. These also benefited peristalsis, which was at first sluggish because of the small residue after meat. The beneficent value of small residues in the intestines of hypertensive and arteriosclerotic patients deserves accentuation. It seems to diminish or at least delay the chances of cardiac dilatation, cerebral hemorrhage and angina pectoris, which are the commonest causes of death in these individuals.

Uremia has not been observed in pure hypertension, except perhaps when it has caused arteriosclerosis, involving the kidneys in its progress.

Even then uremia is uncommon. Sclerotic changes in the arterial wall, of hyperpietics are certainly bound to occur sooner or later, but may be delayed and diminished in extent by avoidance of additional strain and pressure on all blood vessels and particularly those within the abdomen. Here we can easily secure lessened strain by foods which do not leave large residues and do not ferment to any considerable extent. Animal proteins as a predominant nutrient seem therefore particularly indicated in these cases.

Recently I found additional encouragement for this point of view in two publications by Samuel A. Goldberg, formerly professor of comparative pathology, Cornell University and pathologist of Ithaca City Hospital. These are reports of "animal autopsies performed in 1913-1924 and a reprint on "arteriosclerosis in domestic animals." Summarizing these in a personal communication Goldberg states as follows:

"You will note that there were seven cases of marked arteriosclerosis in the herbivorous animals out of a total number of 546 and only one in carnivora out of a total number of 817. In the latter it was really a periaortitis definitely due to infection."

Since I am not dealing here with direct results of infection on arteries, there is justification in eliminating even this single case in the carnivorous group. Thus we are furnished with an analogy that compels attention. In a group of over 800 autopsies on the carnivora, no arteriosclerosis was found while in the, by 50% smaller, herbivorous group seven cases were

in evidence. This is plainly suggestive that a nonprotein diet aids the formation of arteriosclerosis or perhaps that meat rather prevents it. It seems to me the more probable conclusion, and if true, there is a further corollary apparent, that a predominant protein diet in cases of hypertension may circumvent the formation of its dreaded sequel arteriosclerosis. Though hypertension may be secondary to arteriosclerosis, such cases, however, form a different variety and are beyond the scope of our present discussion. But even in these cases a high protein diet may be of benefit in checking further progress provided the renal system is yet competent.

The item of salt restriction which figures in my plan of management of primary hypertension cases also calls for some consideration. I noticed that any salty dish or adding of salt to my food at the table invariably resulted in general discomfort, headache and sometimes dizziness. There are, of course, individual differences as to salt tolerance. But in former years I was fond of salted foods and ate them with impunity. I therefore eliminated this condiment from my diet and was agreeably surprised at the wholesome result. Later I tolerated a slight addition of salt in the cooking, but whenever there is an excess of it I am subject to the same disagreeable symptoms which were mentioned above.

With a high protein diet, salt requirements seem to be lessened. When vegetables form the largest item of a diet the need of it seems increased. The TOUNGUSES and OSTIACS, two tribes that live almost entirely on meat, do well without salt. The harm

## Management of Essential Hypertension

done by the accumulation of salt in our tissues is generally well known. It favors the formation of edema in cellular tissue and serous cavities.

The reason for the use of liberal amounts of acidulated fruits was mentioned in the outline. Not only may they serve as an efficient antidote to the large meat intake, but through their large content of water readily quench thirst in much smaller amounts than would be required to attain the same purpose with other fluids. It is generally acknowledged that the intake of liquids must be restricted in hypertension and cardiovascular disease.

According to Pascaul water contained in fruit possesses particular properties, radio-active perhaps, analogous to that of mineral waters at springs. Fresh fruit is also laxative, but should be partaken peeled, because the large amount of cellulose in the covering may irritate the stomach and like vegetables prove a burden to the splanchnic vessels, which should be avoided.

Coffee and its alkaloids have a permanent and important place in the treatment of acute circulatory failure. But as a beverage we are often warned against its excessive use lest it produce nervousness, insomnia, functional cardiac disturbances and increased tension. Personally, I never experienced these symptoms even after drinking eight cups per day and one just before retiring. Nor did my hypertensive patients report such symptoms with a smaller use of this beverage. One patient definitely refused this adjuvant as he thought that coffee always made him worse. I then substituted twenty grains of caffein

benzoate per day in a watery solution for a considerable length of time without any disagreeable symptoms appearing. If we recall that each cup of coffee as usually served contains two grains of caffein, then twenty grains of caffein in twenty-four hours are the equivalent of ten cups. Therefore the symptoms which that patient dreaded were purely imaginary.

I wish to point out that the value of coffee in hypertension rests not only on empirical evidence but also on well authenticated experimental data coming from physiological laboratories. Thus C. V. Anrep from the Department of Physiology and Biochemistry, University College, London, and Physiological laboratory, Cambridge, in a report which appeared in the *Physiological Reviews*, Vol. vi, No. 4, of October, 1926, on the Regulation of the Coronary Circulation, states that caffein produces a lasting increase in the coronary blood flow. This drug was the only one which produced a *lasting* effect. Such fact seems all important when we consider the use of coffee in cardio-vascular disorders. In primary hypertension the safety of our patients lies in a physiological hypertrophy of the heart and perhaps the muscular coats of the arterioles. A lasting increase in the coronary blood flow is the only means of securing this result. Similar effects may be produced through exercise in the general musculature of the body as well as the heart, but in our cardio-vascular patients the therapeutic application of exercise is very limited indeed.

When the usefulness of coffee and its alkaloids is thus established on a

scientific basis, our cardio-vascular patients are ill served by decaffeinated coffees. The picturesque advertising placards which carry the slogan "Use Sanka Coffee and Save Your Heart" form a real menace to them.

Another fallacy in the traditional treatment of essential hypertension and a similar menace is the custom of sweating and the use of hot baths. These invariably depress the circulation through general vascular relaxation. The temporary lowering of blood pressure does not at all compensate for the concomitant result on the heart. The more relaxed the blood vessels become, the slower is the current within. This is a well established fact in hydrodynamics. With the same force behind a column of fluid the latter flows faster through a narrow tube than in a wider one and with less friction against its walls. Vital centers suffer from this slowing of their capillary blood supply and demand increased work by the heart, either through frequency or force, which often results in minor decompensations. Pulmonary congestion and coughs frequently follow hot baths in hypertensive patients. This is usually ascribed to catching "cold." But in my opinion they are evidences of a low grade cardiac decompensation, like the winter coughs of chronic cardiopaths. Such minor insults to the cardiac muscle are usually cumulative and hasten the final result of a grave left ventricular dilatation. It is scarcely realized what extra load on a heart a full hot or very warm bath represents. Besides the relaxation of the vessels, the slowing of the current and the increased friction

within, there is an increase of surface tension on the venous flow, which equals to nearly four pounds per gallon of water. As a full bath contains about thirty gallons this increased tension amounts to one-hundred-twenty pounds, which directly forms an additional burden on the heart muscle.

I therefore advise against bathing in cases of hypertension. Cleanliness is maintained through luke-warm or cold showers of short duration instead. In addition a cold shower over head, neck and face every morning is strongly urged. The revivifying effect of a cold towel or a cold spray over the face and neck in cases of syncope or after anesthesia is well known. It has been claimed that the thoracic ganglia are stimulated thereby. This effect, so beneficial when needed acutely, lends itself well for continued tonic results if used daily.

The elimination of fats or their reduction to an unavoidable minimum in the dietary of hypertensive patients, seems to me advisable because they readily cause intestinal disturbances and are apt to overload the food intake on account of their high caloric value. When the blood plasma becomes overcharged with fats, they also slow the stream of blood cells, thus enhancing thrombosis by blocking the capillary flow.

Besides these empirical observations with reference to fats we know that the earliest beginning of arteriosclerosis shows fatty deposits in the arteries, where also connective tissue cells and wandering cells are found to be loaded with fat. These form the basis for subsequent atheromatous necrosis through deposits of lime

salts and saponification. Thus the avoidance of fats seems sufficiently justified in these cases.

I believe that all the above mentioned provisions in the management of primary hypertension are imperative if the insidious process of arteriosclerotic formation and its sequelae are to be delayed or favorably modified.

In the more advanced stages of this condition they still seem to me applicable in the absence of special contraindications. But in all the phases of this chronic, but surely progressive disorder, we may add many years of comfortable living through the plan which I outlined, though some modification may be called for in certain cases.

It may not be amiss also to accentuate the necessity of guarding these patients against psychic disturbances and irritating environments. The heart seems more vulnerable in hypertension than in any other disease. Working under the strain of the heightened blood pressure, its excitability becomes more acute. The heart's resistance depends on very low excitability.

A heart removed from the body in lower animals survives the longest when it comes from one of lowest excitability. Since left ventricular decompensation is the most frequent result of hypertension, the necessity of guarding this organ against all possible injury, psychic as well as physical is self evident.

While in angina pectoris we all recognize that mental emotion is a most potent cause in bringing on a paroxysm and sometimes death, we

are apt to forget that this is but a cumulative pathological effect of cardio-vascular disease in which hypertension is a frequent factor. Even in the early stages of the latter precordial discomforts are frequent and are more often than not precursors of the advanced paroxysms of angina pectoris. I casually felt them before the adoption of my regimen and could fully sympathize with John Hunter when referring to his attacks of angina pectoris he stated that "his life was in the hands of any rascal who chose to annoy and tease him." Though I was never in such danger my own attacks were sufficiently unpleasant to bear out this classic comparison.

I presented thus far the dietetic and hygienic management of primary hypertension without reference to the lowering of blood pressure and its medication.

There is a disagreement of opinion on the desirability of such a procedure. However, we would all welcome a drug which should bring about a lasting reduction. So far no such medication has been invented. I have tested in my clinic and private patients liver extracts and failed to obtain the results which have been ascribed to them. Temporary reductions sometimes occurred. I have also tried 20% glucose solutions by vein with similar results. The nitrites still hold first place when a blood pressure lowering drug is indicated temporarily.

I have noted, however, that the method which I have outlined, occasionally produces a permanent lowering, though it failed to do so in my own case. But in all instances this plan has resulted in the abolishment

of the most disagreeable symptoms which accompany essential hypertension, such as headache, fatigue, heartburn, precordial distress, intermittent claudication and minor decompensations. The extent to which it may delay or alter the formation of arteriosclerosis cannot be predicted, though I have reason to conclude from data I have quoted, that it will do so considerably.

Myself and those patients who submitted to this regimen can testify to a sense of well-being which was never experienced on a vegetarian diet with periods of starvation, on purgation, sweating and enforced retirement or rest. Such a treatment not only must fail to prolong life, but also kills all desire to live.

The plan which I have adopted and herein describe even though it may not

add years of life to the victim of hypertension, invariably creates a desire to live and enjoy those years which fate has left him.

#### CONCLUSION

(a) A definite regimen for the management of Essential Hypertension is described, based mainly on a high intake of animal protein and fruits, ingestion of considerable amounts of coffee, avoidance of minor decompensations by the elimination of hot baths with sweating, and the substitution of showers.

'b) Personal experience with this method is related by a physician who is himself a victim of hypertension.

(c) Laboratory and empirical observations are discussed and directed to defend this method.

# Late Spring or Summer Hay-Fever in the District of Columbia and Vicinity\*

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THERE are three distinct types of seasonal hay-fever in the District of Columbia and vicinity, namely: early spring, due to tree pollens; late spring or summer, the type under consideration; and the fall variety, due to the pollen of the ragweeds. From a careful analysis of the case records of all the seasonal hay-fever patients who consulted me during the past year, I would estimate that in the District of Columbia and vicinity, the late spring or summer cases are about eight times as frequent as the early spring type, but only half as frequent as the fall variety. About one-fourth of the late spring or summer cases are of the combined summer and fall types. About 40 percent of the late spring or summer hay-fever victims develop asthma at some time during the course of the disease, whereas about 50 percent of those with fall hay-fever develop asthma.

## ETIOLOGY

The late spring or summer hay-fever season in the District of Columbia and vicinity is from about the tenth or middle of May until the fourth or mid-

dle of July or occasionally the first of August. It is commonly spoken of as "rose cold" or "rose fever," but these are misnomers, as roses are seldom, if ever, the cause. For the pollen of any particular plant to be the cause of true hay-fever it must be floating around in the air in sufficient abundance to be breathed in with normal respiration. In other words, only wind pollinated plants can be held responsible for hay-fever. Clover, daisies, dandelions, honeysuckle, roses, and all other brightly colored flowers with sweet odors are insect pollinated. Even if a person should happen to be sensitive to rose pollen, which is rare, symptoms of hay-fever could be produced only on intimate exposure to roses, and would be more or less transitory.

When I first started to do hay-fever and asthma work, I tested every hay-fever patient with a large number of different pollens, insect as well as wind pollinated. I learned from this that nearly all (about twelve-thirteenths) of the late spring or summer hay-fever patients from the District of Columbia and vicinity were definitely sensitive to the pollens of the following five grasses in varying degrees: sweet vernal (*Anthoxanthum odoratum*), June or Kentucky blue (*Poa pratensis*), orchard (*Dactylis glomerata*),

\*Read before the American Therapeutic Society, May 14, 1927.



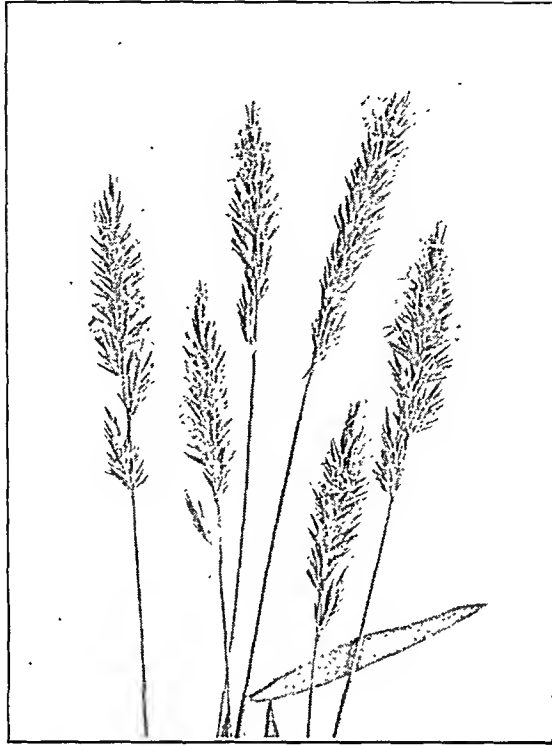


FIG. 1.—Sweet vernal grass (*Anthoxanthum odoratum*).

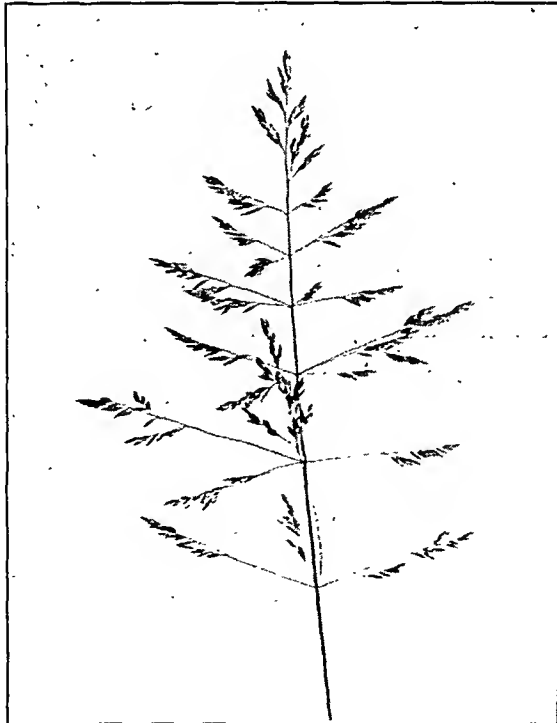


FIG. 2.—June of Kentucky blue grass (*Poa pratensis*).

timothy (*Phleum pratense*), and red top grass (*Agrostis alba* or *palustris*). A relatively small number (about one-sixth) of the late spring or summer hay-fever patients reacted to the pollen of English plantain also known as buckhorn (*Plantago lanceolata*) and a few (about one-tenth) reacted to both plantain and grasses. The five grasses referred to, pollinate successively in the order named, sweet vernal commencing the second week in May, June grass the third week in May, orchard the fourth week in May, timothy and red top the second week in June. The grasses continue to pollinate until about the middle of July. Plantain begins to pollinate about the same time as the grasses and continues until about the first of August. In other words, the period of pollination of the five grasses and plantain coincides exactly with the late spring or summer hay-fever season in the District of Columbia and vicinity. Furthermore, these grasses and plantain grow in great abundance in this locality, and are wind pollinated. Their pollen grains being light and dry, are floating around in the air in large numbers, and under favorable conditions are carried long distances by the wind.

I am convinced that there are a few late spring or summer hay-fever or asthma patients, who are not sensitive to any pollen, food, or animal epidermal, but whose trouble is due to bacteria. This bacterial type of seasonal hay-fever may be differentiated from true pollen hay-fever by the following: definite eye symptoms are usually absent; symptoms are not usually limited to the period of pollination of

grasses or plantain; nasal secretion is more likely to be thick, and yellowish in color; symptoms are usually worse on damp, rainy days; negative cutaneous, intradermal, ophthalmic, intranasal, and hypodermic tests with grasses and plantain. In these patients, proper autogenous vaccine therapy is of course indicated. The method of selecting the organism or organisms to be used, by means of intradermal autogenous vaccine tests, has been dealt with fully in another article (1).

#### DIAGNOSIS

*History.* The symptoms of hay-fever are so well known that I need not describe them. The diagnosis of true late spring or summer hay-fever is made partly by the history of the case, which is somewhat as follows: symptoms of hay-fever occurring annually between May tenth and August first, which symptoms are worse on dry, sunny, dusty days than they are on damp, wet, rainy days (rain tending to wash the pollen from the air); worse in the early morning hours, due to the greater amount of pollen in the air at this time; aggravation of symptoms by proximity to tall grass, likewise worse in the country than in the city; definite aggravation of symptoms from a train trip or an automobile ride through the country; relative or complete freedom at the seashore except when there is a land breeze; complete freedom during an ocean voyage. In contrast to the fall or ragweed cases, the patient with late spring or summer hay-fever cannot obtain freedom by going to Europe. As a matter of fact,

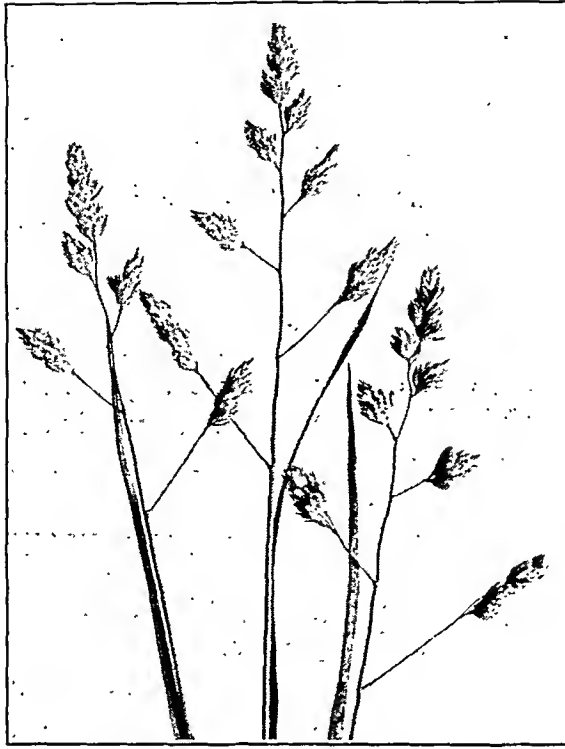


FIG. 3.—Orchard Grass (*Dactylis glomerata*).

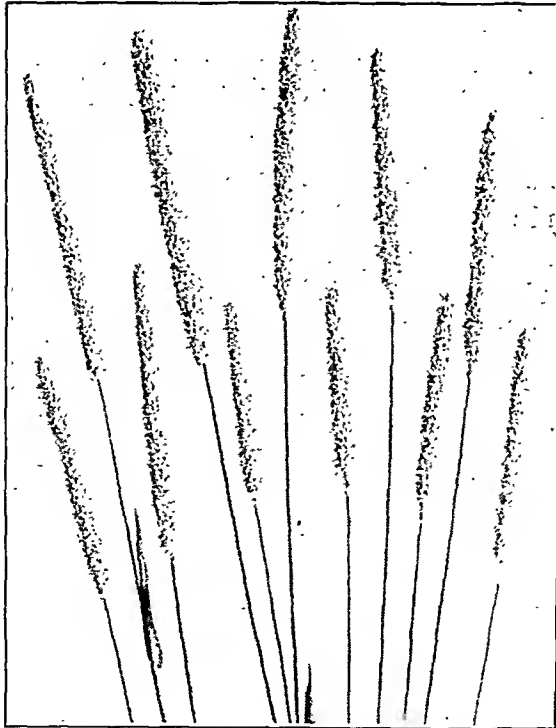


FIG. 4.—Timothy grass (*Phleum pratense*).

grass hay-fever is the prevalent type in Europe and England.

*Skin Tests.* The diagnosis of true late spring or summer hay-fever, suspected from the history, is confirmed by means of skin tests, the technic of which has been repeatedly described. I am absolutely opposed to the intracutaneous or intradermal method for routine testing, for a number of reasons, chief among them being: it is somewhat painful, it gives a number of non-specific or false reactions, and it is dangerous (severe constitutional and even fatal reactions have been reported). The cutaneous or scratch (a minute linear incision is preferable to a scratch) method, on the other hand, is practically painless, does not tend to produce non-specific reactions, and is perfectly safe even with the most sensitive patient. The ophthalmic test is less sensitive than the skin test and is seldom employed today. In testing for pollen sensitivity, I have found it more satisfactory to use the pure dry pollen instead of pollen extracts. A small amount of each of the pollens to be tested is applied to a separate scratch on the patient's arm and dissolved with a drop of tenth-normal (0.4 per cent) sodium hydroxide. Of course, when it is desired to determine the degree of sensitivity of a patient to any pollen, it becomes necessary to test the patient with different dilutions of the specific pollen extract.

Other than pollen, every substance (food, animal epidermal, etc.) should be tested, to which the slightest suspicion can be obtained in the course of an exhaustive history.

#### POLLEN EXTRACTS

When I started to treat hay-fever, I used alcoholic-saline pollen extracts as advocated by Walker (2). After innumerable comparative tests, however, I became converted to glycerine pollen extracts, and am now using them exclusively. The chief point of superiority of the glycerine extracts is their stability. I learned by experience that aqueous or alcoholic-saline pollen extracts rapidly lose their strength, whereas glycerine extracts seem to retain their full potency for at least one year from the date of extraction. Clock (3) was the first to advocate the use of glycerine pollen extracts, his extracting fluid consisting of two-thirds glycerine and one-third saturated salt solution. I personally prefer, as recommended by Armstrong and Harrison (4), to substitute a buffered salt solution (Coca's fluid) for the saturated salt solution, as it is definitely less irritating to the tissues; in fact the individual doses of such an extract (67 per cent glycerine and 33 per cent buffered salt solution) may be injected without further diluting them at the time of injection with distilled water or normal saline. The buffered salt solution may be made by adding 2.7 grams of sodium bicarbonate and 5 grams of sodium chloride to 1,000 c.c. of distilled water. This solution will not stand boiling, and must be sterilized by Berkefeld filtration.

It is desirable to prepare the extracts as concentrated as possible, in order that the very strong doses which are necessary for perfect results, may be administered to patients without injecting large quantities of fluid. As

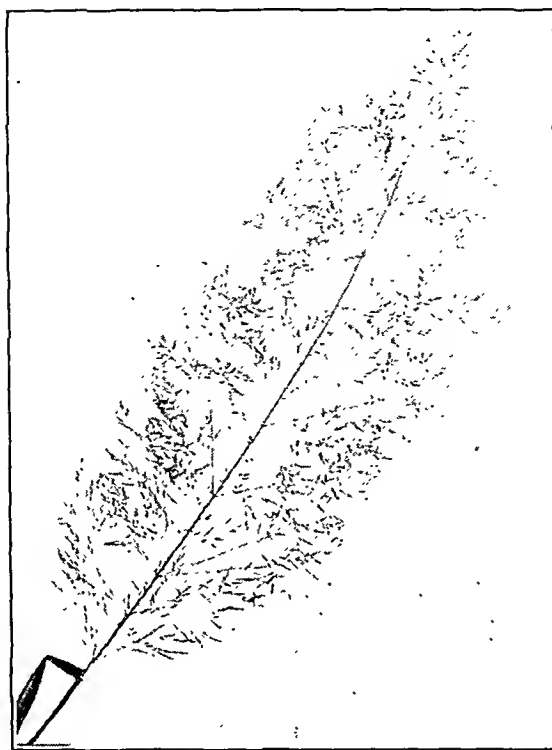


FIG. 5.—Rep top grass (*Agrostis alba* or *palustris*).



FIG. 6.—English plantain or buckhorn (*Plantago lanceolata*).

far as nitrogen determinations are concerned, it seems that 3 per cent pollen extracts are about as strong as can be prepared, using the glycerine extracting fluid described. By a 3 per cent pollen extract is meant 3 grams of pollen to 100 c.c. of extracting fluid. Noon (5) designated the equivalent of one-millionth of a gram of timothy pollen as one pollen unit. It has since been applied, however, to all types of pollen. In other words, 1 c.c. of a 3 per cent pollen extract would contain 30,000 pollen units or 30 milligrams of pollen. In preparing pollen extracts, it is advisable to add some solid glass beads or agate marbles (depending upon the quantity of extract), not with the idea of macerating the pollen grains which is unnecessary, but to facilitate shaking and prevent clumping, and thus allow the extracting fluid to come into contact with all of the pollen. The extracts are allowed to stand for about a week with frequent, vigorous shaking, then Berkefeld filtered, and examined for sterility. Weaker dilutions are then prepared from this concentrated extract by diluting it 10, 100, and 1,000 times. These dilutions are prepared by taking nine parts of extracting fluid and one part of pollen extract to make the next weaker dilution. For the sake of convenience, I designate these three dilutions and the concentrated extract as A, B, C, and D strength respectively.

A—30 pollen units or 0.03 mgms. of pollen per c.c.

B—300 pollen units or 0.3 mgms. of pollen per c.c.

C—3,000 pollen units or 3.0 mgms. of pollen per c.c.

D—30,000 pollen units or 30.0 mgms. of pollen per c.c.

#### TREATMENT

It has been maintained by Scheppegrell (6) and others that treatment with timothy pollen extract would suffice for all forms of grass pollen sensitization. I am opposed to this view for several reasons. In the first place, I consider that patients should be treated with an extract of the pollen or pollens that are the cause of their trouble. Now, in the District of Columbia and vicinity, timothy does not pollinate until the second week in June, and yet the grass sensitive patients, as a rule, start to have definite symptoms the second or third week in May. These early symptoms must be due to the early grasses, and therefore I claim they should also be included in the treatment. Furthermore, it is generally agreed that when the extract of a single pollen is to be used for treatment, the dominant reactor should be the one selected. Certainly, in this locality at least, timothy is not always the dominant reactor, as I frequently test patients whose dominant reaction is to any one of the other four grasses already referred to. I therefore consider that the most satisfactory extract for treating grass hay-fever in the District of Columbia and vicinity, consists of equal parts of the five grasses under consideration, namely, sweet vernal, June, orchard, timothy, and red top. Of course, those patients whose hay-fever is due to plantain, are treated with an extract of plantain pollen, and those whose hay-fever is due to both grasses and plantain are treated with

extracts of each simultaneously, one in each arm.

*Pre-Seasonal.* There are two kinds of treatment, pre-seasonal or preventive, and co-seasonal or treatment given during season. Pre-seasonal treatment started far enough (about two to four months) in advance of season to get the patient as completely desensitized as possible just before pollination of the grasses or plantain, is undoubtedly the ideal method of treating late spring or summer hay-fever. The treatment consists of a series of gradually increasing doses of the specific pollen extract injected subcutaneously in the upper, outer arm. I am of the opinion that the doses can be increased more rapidly by giving them all in the same arm than by alternating the arms. The treatments are given at irregular intervals (from a day to a week apart) depending upon the duration of the local reaction, the general rule being that treatment is not to be given until reaction from preceding dose has entirely disappeared. The individual doses of extract must be measured with extreme accuracy, a tuberculin syringe being necessary for this purpose. The initial dose of pollen extract is usually 3 units (0.1 c.c. of A strength), and each subsequent dose is regulated by the amount of local reaction from the preceding one. In the average patient, the doses can be doubled each time on the weaker dilutions (A, B, and C strengths). Every patient is instructed to carefully inspect his arm about the site of injection at bedtime of the treatment day, and again the following day about 24 hours after the inoculation, to see whether

there is a pink spot on the arm and if so, about how large each time, also to note whether there is any itching or swelling of the arm both times, and to report for another treatment as soon as reaction has completely disappeared. As a rough guide, it may be said that if any individual dose fails to give a satisfactory local reaction (erythema, itching, or swelling, 24 hours after treatment) the next dose may be more than doubled. If positive at bedtime but gone entirely in 24 hours, the next dose may be increased two and one-half times; if no local reaction at any time, the next succeeding dose may be increased three times. If any dose causes a severe local reaction (erythema or swelling extending below the elbow), the same dose should be repeated for the next treatment and then increased less rapidly following that. If a constitutional reaction should follow any treatment, namely, hives, or an attack of hay-fever or asthma,  $\frac{1}{2}$  to 1 c.c. of adrenalin chloride 1:1,000 solution should be injected subcutaneously at once, and repeated if necessary. With proper care in regulating the doses, however, constitutional reactions rarely ever occur. Special care must be used when changing from C to D strength, and in fact with all injections of the concentrated extract, where every 0.01 c.c. is equivalent to 300 pollen units. In administering doses of D strength, we must never consider doubling, but should regulate them instead by the amount of increase measured in pollen units or hundredths of a cubic centimeter. For example, if an increase in dose of 300 units fails to give a satisfactory local

reaction, the next dose should be increased by 600 units, and so on; but if any particular increase in dosage gives a satisfactory reaction, then the next dose should be increased by the same amount.

I am convinced that constitutional reactions are due at times to the needle accidentally entering a small vein or capillary, the extract thus being injected directly into the blood stream. When this occurs, the patient develops constitutional symptoms almost instantaneously. As a precaution against this, after the needle is inserted beneath the skin and before the extract is injected, the syringe piston should be withdrawn sufficiently to see an air space between the extract and the rear end of the needle, and if a trace of blood shows in this space, the needle should be withdrawn and inserted in another spot before injecting the extract. All injections should be made slowly. Following the stronger doses, the patients should be kept in the office for awhile, about 15 minutes for C and about one-half hour for D strength. The advantage of keeping the patients in the office is that, if constitutional symptoms begin to develop, such as itching of the palms of the hands or irritation of the throat or nose, adrenalin may be administered without delay, thus checking the reaction or greatly reducing its severity. Furthermore, constitutional reactions are not so likely to occur if the patients remain quiet for awhile, as exercise, especially in hot weather, increases the circulation and therefore causes the pollen extract to be more rapidly absorbed.

The maximum dose of pollen extract

that I seek to attain just before pollen season is from 15,000 to 30,000 pollen units (0.5 to 1 c.c. of the 3 percent extract). Whatever maximum dose is reached just before pollen season, is repeated at weekly intervals throughout the season to keep the patient as completely desensitized as possible.

*Co-Seasonal.* For those patients who present themselves for treatment just before or during the hay-fever season, co-seasonal treatment with specific pollen extract is clearly indicated. The initial dose of pollen extract is the same in co-seasonal as in pre-seasonal treatment, usually 3 units. In co-seasonal treatment, however, instead of regularly increasing the dose, the smallest dose is given throughout the season that will produce a satisfactory local reaction (erythema at least the size of a dime, 24 hours after treatment), and only increased when it fails to produce such satisfactory reaction. Co-seasonal treatments are given at irregular intervals, from a day to a week apart, depending upon the amount of relief obtained from the individual treatment. Each patient treated co-seasonally is instructed at every treatment that if he receives no benefit from that particular treatment, to report the next day. If relief follows any individual treatment, however, he is instructed not to report for further treatment, until he begins to slip back, or in other words, until the effect of the treatment begins to wear off.

In a previous article (7). I stated that the use of bacterial vaccines seemed to me to be illogical and useless in the co-seasonal treatment of typical



pollen hay-fever, but I have since been forced to modify my views on this point. I find the use of a stock mixed "cold" vaccine containing the common respiratory organisms, in addition to the specific pollen treatment, a valuable aid in the co-seasonal treatment of hay-fever. Scheppegrell (6) and others also recommend the use of bacterial vaccines co-seasonally. It is my opinion that a pollen treatment should never be given while there is any visible reaction from the preceding pollen treatment, although a vaccine treatment may be given at such time in the opposite arm. I give 0.1 c.c. as the initial dose of vaccine. If this gives a satisfactory local reaction, and it is necessary to give additional vaccine treatments, I repeat the same dose. By a satisfactory local reaction from vaccine, I mean a pink spot at least the

size of a dime ( $\frac{3}{4}$  inch) visible 48 hours after treatment. The same rule applies to vaccine treatments as to pollen treatments, namely, not to give an injection of vaccine as long as there is any visible reaction from the preceding vaccine treatment. If 0.1 c.c. of vaccine fails to give a satisfactory local reaction, I try 0.2 c.c., etc. In other words, I seek to obtain a satisfactory local reaction from every co-seasonal treatment by giving the smallest dose that will produce such satisfactory reaction.

When the diagnosis is correctly made, and the treatment (pre-seasonal or co-seasonal) properly administered, the results are almost invariably successful, namely, complete or practically complete relief from hay-fever, regardless of the age of the patient, or the duration or severity of the disease.

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# The Quest of the Holy Prepuce\*

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EVER since the unfortunate escape of all manner of diseases from the mythical box of Pandora, men have, through one means or other, attempted their cure. Whether through the savage incantations of voodooism, or through the various noxious potions used in the middle ages, or through knocking the devil literally and figuratively out of the patients as done by some tribes and even by the Puritans, or by means of the various cure-alls, manipulations, psychotherapy, ecclesiastical and otherwise, or through the spectro-chromotherapy of Ghaduli, or the magic hocus-pocus oscilloclastic box of Abrams, not forgetting the medicated gum drops, chewing gum, etc., men have put forth their claims for treating all of the ills that man is heir to. It was ever thus, and as long as disease is the portion of man, science, near-science, pseudo-science and non-science will battle the common cause, each to register its claims of superiority. Man by nature has always been more or less inconsistent. This claim, I realize, was supposed to be the privilege of woman, but it goes without saying she has her counterpart in man. What man finds good, and to his liking, he naturally approves of; what he questions, may be approved

of later and even adopted. Thus we gain knowledge and the application of knowledge.

At no time was man more zealous of curing the ills he knew little about or more jealous of his contemporaries than in the Middle Ages, when not only were powdered mummy, toads and other appetizing medicaments used for the alleviation of disease, but also the desire for miraculous healing was at the zenith, which prompted the pious and well-meaning clergy to collect, conjure, or cause to be made, relics of departed saints, which were understood to be imbued with supernatural powers for the healing of the sick. Consequently fetish worship became prominent, the popularity of which was nearly as great as that of "Abrams' Oscillator." So great was the demand for various relics that several monasteries and cathedrals, widely separated, claimed to possess the one and only genuine article.

In no case was a relic more venerated than that of the Holy Prepuce.

Circumcision has been practiced by the Jews ever since Abraham and his household of four hundred males were circumcised at Chaldea as a covenant of faith with God. The Mohammedans, who are equally zealous circumcisers, date their practice back to the father of their race, Ishmael, the son of Abraham and his handmaid Hagar,

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who was circumcised by Abraham at the age of thirteen. Yet neither the Jews nor Mohammedans went to the lengths reached by the early Christians, who, strange to say, abolished and repudiated the rite of circumcision, and even persecuted the Jews because of it, yet were inconsistent enough to celebrate its performance with the Feast of Circumcision, and considered its occurrence of sufficient merit to be used as a memorial to excite veneration for the church and promote the pious zeal of the faithful.

Whether or not the quest for relics, so prevalent in Europe in the Middle Ages, was wholly for the purpose of proselyting, or because of medicinal or miraculous value, is a question not satisfactorily answered.

During the 13th and 14th centuries, the Abbey Church of Coulomb, in the diocese of Chartres, France, became possessed in some unknown mysterious manner, of the Holy Prepuce, which it was said possessed the infallible power of rendering all sterile women, who worshipped it, fruitful, and assured easy birth. Naturally such a virtue filled the benevolent monks of the Abbey with a great but pardonable amount of pride. Such virtues are not commonly met, consequently this augmented the numbers of the faithful and added to the reputation and vanity of the monks. Unfortunately for the monks, the popularity of the prepuce became so widespread that they nearly lost their relic.

The good and valiant King Henry V of England and a part of France, was exceedingly desirous that his Queen should have assured an easy birth with the much desired heir.

Naturally, hearing of the efficacy of the Holy Prepuce, he decided to go to Coulomb after it. The unannounced visit of such an august royal personage at the Abbey gates threw the monks into a state of consternation, especially so when his Royal Highness asked for a loan of the prepuce in much the same manner that Mrs. Smith would ask for a loan of a cup of sugar. Refusal was out of the question, and Queen Catherine, of France, feared King Henry as being too powerful to be put off. Inasmuch as evasion did no good and there was no time for duplication, nothing was left for the poor monks to do but reluctantly part company with their prize remunerative possession. When received King Henry caused it to be taken by royal convoy to London, that his waiting Queen might but touch it and insure safe delivery.

Honest Henry fully intended to return the relic immediately after it received the Queen's touch and served its purpose, but, being human, he realized its market possibilities. Therefore, instead of returning it, he caused a royal sanctuary to be built for its repose, where it remained for twenty-five years, regardless of the repeated quests and supplications of the monks for its return to Coulomb. One can imagine the great amount of sterility and maternal distress caused by its absence. There was great rejoicing, however, when, like the prodigal son, it finally came back, and especially so when it was found to possess all of its virtues. Truly the people and clergy had every reason to rejoice, knowing that at least the spectre of fear of a deci-

mated population and maternal agony, had at last been removed.

Even as in our present day life, the genuine is not without its imitations, so it was the case with the Holy Prepuce. Several other places, knowing of its fame and popularity, claimed the honor of having the original prepuce. The Cathedral of Puy in Velay, the Collegiate Church at Antwerp, the Abbey of Our Savior of Charroux, and the Church of St. John Lateran, in Rome, all vied with each other in popularizing it.

The Abbey of Charroux was founded in 788, by Charlemagne, who endowed it with a fragment of the Holy Prepuce. From whence it came is not stated. This Abbey, however, became so popular that indulgences were granted by the papal bull, to all who assisted in the worship of its relics.

During the internecine wars of the 16th century, this Abbey fell into the hands of the godless and heretical Huguenots and the Holy Prepuce disappeared. Since you can not keep a good thing down, when the workmen demolished the walls in 1856 for a new Abbey site, lo and behold! a relic box was found, in which the good bishop found the long lost prepuce, which he carefully placed in charge of the Ursuline Sisterhood, where it was supposed to have remained ever after. Apparently the good bishop of the Church of St. John Lateran in Rome thought differently, for he claimed to have the only authentic Holy Prepuce in his possession. This disappeared during one of the periodical sackings of Rome by the Goths, Vandals and Christians. During the sacking of Rome in 1527, it is related, a soldier

ran away with the holy box. This impious wretch, it is said, came to grief, and some mysterious force compelled him to secrete the box when a short distance from Rome, where it remained for 30 years, when a priest happened to stroll that way and found it. He immediately carried it to the lady on whose domain it was found. On being opened it was found to contain a piece of anatomy of Saint Valentine, the lower jaw of St. Martha, with one tooth intact, and a small package on which the name of the Savior was inscribed. The lady who opened the box stated that a most fragrant odor permeated the atmosphere, also that there was a decided swelling and stiffening of the hand that held the box. Investigation, of course, once more proved it to be the long lost and much sought for prepuce, hence another occasion for rejoicing.

It is said that an inquisitive mind will sometimes cause vexation of the spirit. Such was the case with the pious Canon of the Church of St. John Lateran, who let his curiosity get the better of him and almost caused a well-deserved catastrophe. Being prompted to investigate, he unwisely broke off a piece of the prepuce, when instantly chaos ensued. A terrible tempest broke over the place. Loud peals of thunder and blinding flashes of lightning, with a sudden darkness of Stygian variety, covered the country, voicing the indignation of these perturbed elements, and thereby wrought such a state of fear in the luckless priest and his assistants that all straightway fell down upon their sacerdotal noses fearful of the judgment.

Veiled mysticism has shrouded many an uncertainty, and baffled the material mind for solution, and woe unto the doubting Thomas who failed to accept, without question, that given him by the sanctified clergy of medieval times. What they said was so because they said so, hence the satisfied obedient people accepted the crumbs given them without question, enthralled by the infallible potency of their ecclesiastical custodians. Sacred edifices for worship and healing were built because of some ecclesiastical mandate, made known through man or beast, and heretical was he who as much as questioned the authenticity thereof.

It is related that at one time a sacrilegious soldier robbed one of the churches near Turin, and rode his donkey to this city to dispose of his ill-gotten gain. On arriving there a consecrated wafer ascended out of his plunder and stayed suspended above the soldier unknown to him, thereby attracting the attention of the populace and the good bishop. The donkey, being more imbued with piety than his master, knelt, regardless of his master's blows, until the bishop drew near, when the wafer graciously descended into the bishop's pious hands. Consequently the soldier was immediately hanged for his rash act, and the donkey adopted into the brotherhood. So well behaved and sanctified a beast must naturally be honored, hence the Church of Corpus Christi, in Turin, was erected on the exact spot where the donkey knelt. Moreover, in the center of this edifice was a large flagstone, protected by railing, for the use of the devout.

If, as has been shown, the Holy Prepuce was such an important factor in the consolidation of religious thought, and for the amelioration of mental and physical suffering, one would logically conclude that the instrument for removing the prepuce must also have intrinsic value, therefore should be possessed by some enterprising party. What was needed somehow or other was supplied, hence it was not long after the prepuce popularity was at its height, that the convent of Saint Corneille, in Compiègne, announced the possession of the identical instrument used to perform the Holy Circumcision.

In addition to preputial worship the clergy had taken over the old phallic worship of the Gauls, whether as a means of converting the heathen Gaul, through the adoption of a well established practice, or because of the supposed merit associated with phallic worship, is not clearly understood. Nevertheless, phallic worship was exceedingly popular in the 16th and 17th centuries, largely due to the zeal and enterprise of the clergy.

It is difficult to determine the original source of phallic worship. Several tribes and races practised it, even to the Romans, as shown by the phallic statues found in the ruins of Pompeii and Herculaneum. According to tradition the god Osiris, on returning to Egypt, found that Typhon fomented dissension during his absence. In the conflict which followed, Osiris was slain, and Typhon dismembered his body, which he gave to his followers, but kept the phallus himself. Later Isis, the spouse of Osiris, secured control of the government, and

collected all of the pieces of the dissected Osiris with the exception of the phallus, Typhon having thrown it into the sea. Isis then ordered that statues be constructed, each to contain a piece of the unfortunate Osiris, but for the phallus special worship was ordered. Thus originated the phallic worship, and the sacredness of the white bull Apis of the Egyptians, the bull being chosen to represent Osiris.

One of the first clergymen sent to Christianize Gaul was Bishop Fountin of Lyon, who later became Saint Fountin. So well did priapic worship commingle with his religious teachings, that somehow or other, St. Fountin and old dethroned Priapus became analogous. Finally the former took the place of the latter, and as a result, became immensely popular. He was believed to have exerted wonderful influence in restoring fertility to barren women, as well as vigor and virility to impotent men. So great was his reputation at the Church of Varages, in Providence, that it was customary to make wax models of the flaccid impotent penile appendages of the devoted, and deposit them on the shrine, that once more youthful virility might be restored.

A large phallus, said to be the relic of St. Fountin, was kept in a church at Embrun, where worshippers could obtain miraculous cures for their sterility, by pouring wine over the head of the organ, and catching it underneath in a sacred vessel. Thus the wine was changed into "holy vinegar," a very efficacious remedy for sterility and impotency.

At the time of the Roman occupation of Gaul there was a large priapic

statue near the city of Bourges, at Bourg Dieu, which was greatly venerated. At first the monks and missionaries wanted to remove it, but this caused such commotion with the Gauls, it was thought best to leave well enough alone. Being desirous of cementing the bonds of brotherhood, and not caring to hurt the feelings of the Gauls, the accommodating clergymen transformed it into a Saint—St. Guerluchon—and made a proclamation that scrapings from this statue infused in water would make a miraculous drink that insured conception. Later, several statues of St. Guerluchon appeared in various places, and the clergy competed with each other in increasing the popularity of their particular shrine. At one of these shrines so onerous became the job of replacing a new phallus, that the monks draped the phallus with a cloth, and made it known that mere contemplation of the sacred organ was sufficient.

Not being desirous of being outdone by their well-meaning brethren, the monks in charge of St. Guerluchon's shrine, near the seaport town of Brest, in Brittany, adopted the novel expedient of boring a hole horizontally through the statue, through which the phallus was inserted, so that as fast as it was scraped away in front the industrious monks pushed it forward from the rear, hence not only was there plenty of phallus to go around, but it promulgated the idea of a miraculous growth of this member. Consequently the reputation of this shrine was established, and they continued to do a flourishing business up to the middle of the 18th century.

In relating the foregoing facts there

is no design, or intent, to belittle or criticise, any particular form of worship or question the efficacy or results obtained. It is said many a miraculous cure was made, whether authentic or not remains to be known. However, it is somewhat baffling to know the intricate and devious route sometimes apparently necessary to effect the cure. Curious facts, at times, are gathered in most unlooked for places, and rags may clothe monumental wisdom. It is said that while Benjamin Franklin was going to town, one day, he happened to pass a farmer who implored him to return home, saying it was going to rain. Inasmuch as the sun was shining, Benjamin thought him half witted, and went his way only to be caught in a downpour of rain. Being of an analytical mind, and regardless of his drenched clothing, he returned to ask the rustic the source of his knowledge. The farmer said, "Whenever it is going to rain, your worship, my cow twists her tail in a certain direction, and I saw her twist her tail just before you came." Of a truth wisdom is golden.

The medical practices of the ancient and medieval folk may be excused on

the grounds of ignorance and superstition, which naturally cannot compare with our superior learning and more complete equipment, yet there is no fatter pasture for charlatanism and at no time was quackery more extensively practiced than in the United States at present. The situation must be met in a sense of fairness. It may be unethical and unorthodox to delve into that considered irregular and unscrupulous, but only through getting in actual touch with the situation, and adopting that of proved merit, and exposing the valueless or harmful methods, will the people, now criticised for patronizing quackery, look up to the medical profession as the guardian of public health, as expected of it.

In so doing we may have to agree with Remondino in that "our ethics will need circumcising—and the prepuce of exclusion should be buried in the sands of the desert."

Repeated gloved challenges have been hurled at the medical association from various cults. The all important question is, will they be accepted and acted on, or will the bone of contention remain?

## Editorials

### The Chemical Regulation of Respiration

THE subject of the control of respiration has given birth to many theories and innumerable investigations. The accumulation of data is great. Repeated experimentation under identical conditions by numerous trained observers has demonstrated the accuracy of various findings. What is lacking is the explanation of these results. Much of the experimental work on the mechanism of respiratory regulation has been planned to test empirical findings, but very little has been carried out to determine the nature of the behavior of nerve tissue. What is needed are basic experiments leading to an explanation of the nature of the institution and conduction of the nerve impulse in nerve and nerve centers. What do we know about the respiratory center; is it automatic or does it function as a reflex center? Is its activity controlled by so-called nervous influences, or by chemical agencies, or by both, and what are the chemical agencies concerned, the hydrogen-ion, carbon dioxide, or oxygen, or unrecognized substances? Is it a concentration of respiratory hormones in the arterial blood that stimulates, or is the metabolism of the respiratory center itself the important factor? What part does the acidity of the blood play, and what is the relation of the latter to the acidity of the interior of the cells of the respiratory center? Is the transport of

acid to or away from the center the controlling factor? What is the relation of the acidity of the blood to the acidity of the interior of the cells of the respiratory center? In what form is carbonic acid carried in the blood, and how across the cell membrane, and what is the significance of the permeability of the cell membrane in the exchange of acid and base between the cell and its environment? What is the significance of the buffer capacity of the cell as well as of the blood? As Gesell has pertinently pointed out, these are the questions that must be answered in the final solution of the problems of respiratory regulation. The views of Haldane and his associates, Winterstein and Hasselbalch, are almost universally accepted today, although the literature shows innumerable exceptions to the principles maintained by them of a correspondence between pulmonary ventilation and the hydrogen-ion concentration of the blood. According to their view the hydrogen-ions of the arterial blood stimulate the respiratory center, thereby controlling its activity, and pulmonary ventilation is so regulated as to maintain a constant hydrogen-ion concentration of the arterial blood. According to Haldane and his co-workers lack of oxygen stimulates respiration by making the respiratory center more sensitive to the ordinary concentrations



of  $\text{CO}_2$ . When there is a sudden lowering of oxygen tension, there is an immediate increase in respiration, since the center is more sensitive to the existing  $\text{CO}_2$  tension. This sweeps out the  $\text{CO}_2$ , and lowers the level of this gas in the blood. When the lower level is reached the increased breathing subsides. This explains why a marked initial hypernea is not seen when the oxygen tension is gradually lowered; there is time for a gradual establishment of a lower  $\text{CO}_2$  level. According to this view the respiratory center is controlled by the hydrogen-ion concentration of the blood even during anoxemia, for even under these conditions the breathing changes accordingly, if the alveolar  $\text{CO}_2$  be increased or decreased. This theory of anoxemia assumes that lack of oxygen *per se* stimulates the respiratory center by rendering it more susceptible to stimulation by the existing  $\text{CO}_2$  tension. It is difficult, however, to explain the continuance of a low alveolar and blood  $\text{CO}_2$  for a considerable length of time after the want of oxygen is relieved. In explanation the lactic acid theory has been adduced. In the presence of insufficient oxygen the processes of oxygenation are not completed but stop at intermediary stages, the chief product of improper oxygenation being lactic acid; and it is assumed that in anoxemia sufficient of this acid is set free in the blood to increase the hydrogen-ion concentration, which stimulates the respiratory center and brings about the increased respiration. Briefly expressed the generally accepted view of respiratory regulation is that lack of oxygen causes an increase in respiration which results in the sweeping off of  $\text{CO}_2$  with a result-

ant low alveolar  $\text{CO}_2$  tension, which in turn produces an alkalosis. The kidneys and liver attempt to compensate for this alkalosis by diminished ammonia and acid excretion and increased alkali output. This compensation, except in slight degrees of anoxemia, is never quite complete, as shown by the continued low  $\text{CO}_2$  pressure. While this theory of the hydrogen-ion concentration of the blood as the regulation of respiration is generally accepted in the present day textbooks as a physiological finality, and pathological disturbances of ventilation and respiration are based upon it, a large body of experimental work is contradictory to the assumptions of the hydrogen-ion concentration theory of respiratory regulation. It is impossible to consider this contradictory work in detail, and we can call attention here only to the very important, and perhaps epoch-making work of Gesell and his associates during the last several years. According to the latter there is at present no positive evidence showing any causal relationship of acidity of the arterial blood to pulmonary ventilation. The inverse relationship is more common than the direct. An approximate constancy of the arterial hydrogen-ion concentration is no proof that the hydrogen-ions of the blood regulate respiration; the hydrogen-ion concentration of the blood may be the result of pulmonary ventilation rather than the cause. If acidity of the respiratory center is the important factor, it is more plausible that the diffusion gradients governing acid-base equilibrium are adjusted to maintain a constant hydrogen-ion concentration of the tissues rather than of their environment, the blood. In that event a lack

of correspondence between pulmonary ventilation and acidity of the blood may find an explanation. Since oxygen tension and carbonic acid tension as well as the hydrogen-ion concentration are regarded as constituting the chief respiratory stimulants in the blood controlling pulmonary ventilation Gesell asks this pertinent question, what is the source of the stimulation of the respiratory increase resulting from hemorrhage. It cannot be an increased tension of carbon dioxide of the arterial blood, because that is markedly lowered. There is a similar reduction in  $\text{HCO}^3$  ions. It cannot be due to increased lactic acid in the blood because the effect is immediate. It is not arterial hydrogen-ion concentration because this is markedly reduced. Nor can it be the arterial oxygen tension because hemorrhage increases the oxygenation of the blood. It is not the hypothetical "respiratory x" of Haggard and Henderson for the existence of which all evidence is lacking. Hypernea is thus left without a single recognized respiratory stimulant to account for it. However, it was not the association of hypernea with the diminution of every known form of stimulation which forced Gesell to question the prevailing theories of respiratory control, but rather the production of apnea in the absence of any chemical change within the arterial blood. This was demonstrated in experiments carried out by Gesell in association with Capp and Foote in which the hypernea of hemorrhage was transformed into apnea by the acceleration of unchanged blood through the respiratory center. They accepted the prev-

alent view that respiration was controlled by the arterial carbon dioxide or hydrogen-ion concentration as a basis for studying the effect of hemorrhage and subsequent injection of gum-saline solution on the volume-flow of blood. They reasoned that if hemorrhage decreases the volume-flow of blood, and if the formation of carbon dioxide in the body continues at the normal rate, the blood should return surcharged with carbon dioxide and free hydrogen-ions which on reaching the respiratory center would stimulate respiration. They reasoned further that if the injection of gum-saline solution accelerated the volume-flow of blood out of proportion to the dilution of the blood the nutrient flow would be increased. The carbon dioxide carriers would circulate at a more rapid rate and consequently would be more lightly laden with carbon dioxide; the hydrogen-ions of the blood reaching the respiratory center would be diminished and respiration would be correspondingly depressed. But the immediate cessation of respiration on the acceleration of unchanged blood, that is, blood which had already left the tissues, forced the conclusion that the metabolism of the respiratory center and transport of acid from the center are the primary factors in the control of respiration. The theory developed by Gesell from these observations is essentially as follows: The respiratory center possesses an acid metabolism of its own. The rate of formation of acid in the center and the rate of transport from the center determine the acidity of the center. Changes in the hydrogen-ion concentration of the respiratory center rather than the blood constitute the

prime factor in respiratory control. Since the supply of oxygen determines the absolute and relative amounts of lactic acid and carbon dioxide found in living tissues, and since it controls the efficiency of transport and elimination of acid, it constitutes the normal and indirect regulator of pulmonary ventilation. The effects of lactic and carbonic acid are additive. They are exerted indirectly by way of the blood from the tissues, and more directly through their formation in the respiratory center itself. Diminished oxidation in the respiratory center leads to an accumulation there of the relatively poorly diffusible lactic acid in a relatively poorly buffered cytoplasm and lymph, no longer fully protected by the potential alkalinity of the blood—the dual function being disturbed by the diminution in the reduction of hemoglobin and the liberation of alkali as it passes through the center. By virtue of its own metabolism and its extreme sensitivity to minute changes in its own hydrogen-ion concentration the respiratory center is sensitive to minute changes in its own oxidations, and therefore, to changes in the oxygen tension of the arterial blood. The capacity of the center to respond to changes in the arterial carbon-dioxide tension, consequent on fluctuations in the general metabolism, however, must also be a factor. Gesell does not claim that the reaction of the tissues of the respiratory center itself as the true stimulus of respiration solves all of the problems of the mechanism of respiration and ventilation. In its ultimate analysis the regulation of respiration may be found to be an electrical phenomenon occurring with the aid of a

surface membrane and changes in composition of the fluids on both sides of that membrane. Whether acid is the only agent which can produce the necessary electrical disturbance involved in the nerve impulses is highly improbable; on the other hand, it may be the agent most employed in the body. The reception of Gesell's theory of the regulation of respiration has naturally been antagonistic in part. Roberts re-investigating the effects of hemorrhage on respiration states that "the fact brought out that pulmonary ventilation does not vary inversely with the blood pressure completely negatives Gesell's assertion and shows that his theory is without experimental foundation." On the other hand, Schneider, Truesdell and Clarke believe that "this theory provides the best explanation for the respiratory variations of the type of anoxemia we have studied." Confirmation of the accuracy of Gesell's theory remains to be furnished by other investigators, and because of the great importance of the problem it is desirable that workers in the field of respiration and ventilation concern themselves with investigations bearing upon this question.

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#### ENTERIC FEVER SITUATION IN THE WORLD\*

The following report on enteric fever in the world is taken from the September 15 issue of the Monthly Epidemiological Report of the Health Section of the League of Nations Secretariat.

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\*From League of Nations Non-Partisan Association, 6 East 39th Street, New York City.

The enteric fever situation was on the whole favorable in July in most European countries. In England the incidence decreased toward the end of July, while fewer cases than usual were reported in July in Denmark, Norway, Sweden and Finland. In England and Wales, there were 321 cases during the four weeks ended August 20, as compared with 406 cases during the previous four weeks, although the incidence ordinarily increases markedly at this time of the year. In Germany, fewer cases were reported in July and early August than during the corresponding months of any previous year. It is to be noted in this connection that exceptionally cool and wet weather prevailed over the northern part of Europe in June and early in July.

Further south in Europe the incidence may be characterized as normal, except in Italy, where it was above normal (2,100 cases during the four weeks ended July 3, as against 1,274 cases during the corresponding period of the previous year). In the Serb-Croat-Slovene Kingdom, the incidence was also higher than last year and there was an outbreak at Belgrade, where 48 cases were reported during the first week of August; it seems to have been promptly controlled, as there were only 10 cases the following week. The crest of the seasonal curve for enteric fever is not reached until September or October, but its low prevalence in summer in many countries is probably of good augury for the autumn.

In the United States, 3,878 cases were reported during the four weeks ended July 30, as compared with 3,493

cases during the corresponding period of 1926.

In Canada, the enteric fever situation is entirely dominated by the formidable epidemic at Montreal. This epidemic, which appeared to be coming to an end in the latter half of April, broke out afresh early in May. There were nearly as many cases in the second wave as in the first. A recrudescence of this magnitude is a most unusual phenomenon.

From the beginning of the epidemic and up to July 9, 4,849 cases were reported and 489 deaths were ascribed to typhoid fever. Notifications numbered 2,604 in March and April, which may roughly be taken to correspond with the first wave, and 2,242 in the second wave between May 1 and July 9. If the deaths reported up to May 7 are taken as corresponding to the first wave, there were 251 deaths during the first and 234 during the second wave. Deaths due to the first wave occurring after May 7 will probably be approximately compensated by those who may have died after July 9, returns for which have not as yet been received. This would give a case mortality rate of 9.6 per cent in the first and 10.4 per cent in the second wave.

The circumstances which produced the second wave were evidently already in operation in the latter half of April, when the notifications showed only the tail-end of the first wave. It may be noted in this connection, that, in 1926, there were 256 deaths from typhoid fever in the Province of Quebec (203 in the remainder of Canada), and that only 271 typhoid cases were reported.

It is confirmed that the origin of the

epidemic was due to milk-borne infection.

The proportion of hospitalized patients is a little over 33 per cent of the total. Convalescents are discharged when two examinations of feces and of urine made at intervals of not less than three days have given negative results.

A high proportion of the cases were among children; 35.5 per cent of the cases for which the age is stated were under 10 years of age and 32.2 per cent between 10 and 20 years.

Mortality statistics are on the whole more complete than morbidity statistics and are therefore more readily comparable for different countries—at any rate, for diseases in case of which the diagnosis does not present too great difficulties. As statistics of causes of death for 1926 are so far available only for a few countries, the enteric fever death rates for 1925 and 1926 are given below for groups of large towns.

	Population in Thousands	Rate per Deaths 100,000			
		1925	1926	1925	1926
107 English towns	19,411	183	140	0.9	0.7
16 Scottish towns	2,396	24	23	1.0	1.0
3 Scandinavian towns	1,300	11	11	0.8	0.8
48 Germany towns	17,024	336	483	2.0	2.8
47 German towns*	16,597	330	223	2.0	1.3
14 Dutch towns	2,411	57	44	2.4	1.8
30 Swiss towns	1,184	16	13	1.4	1.1
2 Belgian towns	1,126	39	22	3.5	2.0
5 French towns	3,932	222	214	5.6	5.4
7 Italian towns	3,447	483	646	14.0	18.7
49 Spanish towns	4,263	890	1,081	20.9	25.4
4 Czechoslovakian towns	1,176	97	84	8.2	7.1
4 Polish towns	1,995	256	308	12.8	15.4
79 Ukrainian towns	3,460	443	528	12.8	15.3
2 towns of the U. S. S. R.	3,632	463	409	12.7	11.3
2 Egyptian towns	1,351	445	438	32.9	32.4
21 Japanese towns	8,741	...	2,325	...	26.3
4 Indian towns	3,128	909	1,057	29.1	33.8
59 towns of the United States	29,621	993	822	3.4	2.8

\*Without Hanover.

It is seen that in Europe the incidence of enteric fever in general increases from north to south; in England and in the Scandinavian countries, the mortality is of less than 1 per 100,000 inhabitants; in German, Dutch and Swiss towns it is mostly between 1 and 2 per 100,000, exception made of the explosive outbreak at Hanover, when the death rate rose to 60.9 in 1926. In southern and eastern Europe the death rates from enteric fever are mostly between 10 and 20 per 100,000: in certain Spanish and Italian towns they exceeded 30. At Athens the rate was 39.3 and at Salonica 44.1 in 1924.

The mortality in European towns was on the whole lower in 1926 than in 1925, with exception of Spanish, Italian, Polish and Ukrainian towns, where the rates were higher.

Similarly in the United States, the mortality from enteric fever is mostly below 2 per 100,000 in the northern towns, but exceeds 10 in most towns of the South. It was on the average lower in 1926 than in 1925.

#### *Mortality in 1926 in Large Towns of the United States Grouped According to Geographical Divisions*

	Population in thousands	Deaths	Rate per 100,000
New England	2,522	38	1.5
Middle Atlantic	11,399	241	2.1
South Atlantic	2,226	120	5.4
North Central	10,596	192	1.8
South Central	2,314	294	12.7
Rocky Mountain and Pacific	3,431	68	2.0

In sub-tropical and tropical countries, enteric fever is even more prevalent than in Southern Europe or in the Southern States of the United States. The mortality per 100,000 inhabitants in 1926 was thus: 38.9 in Cairo, 82.4

in Teheran, 68.9 in Calcutta, 29.1 in Singapore, 35.9 in Batavia and 29.1 in Manila. It is probable that in several of these towns the certification of causes of death is less accurate than in European towns and the rates may therefore in some instances be too low.

In South America, the incidence of enteric fever is lowest in the southern temperate climates and generally increases northward. The death rate from this cause per 100,000 was in 1926: 4.4 at Buenos Aires, 14.2 at Montevideo, 41.4 at Sao Paulo, 8.5 at Rio de Janeiro (low for the latitude), 33.7 at Lima and 92.8 at Bogota.

Mortality statistics for 1926 are available for the countries shown below; the rates do not differ greatly from those given above for large towns in the same countries.

*Mortality from Enteric Fever in Various Countries in 1926.*

	(Population in thousands)	Deaths	Rate per 100,000
England and Wales	39,067	367	0.9
Scotland	4,903	39	0.8
The Netherlands	7,449	137	1.8
Switzerland	3,959	59	1.5
Germany	62,612	1,102	1.8
Czechoslovakia	14,353	1,183	8.2
Spain	22,128	4,747	21.5
Canada	9,291	461	5.0

## Abstracts

*Primary Sclerosis of the Pulmonary Artery and Its Branches.* By C. M. BACON and C. W. APFELBACH. (Archives of Pathol. and Lab. Med., May, 1927).

Primary sclerosis of the pulmonary artery and Ayerza's disease are two clinical entities which have been studied with increasing frequency during recent years. Even though diminution of the pulmonary bed by sclerosis of the pulmonary artery and its branches is the essential morbid alteration in both diseases the clinical manifestations, as described, are in many respects dissimilar. Most authors describe syphilitic arteritis of the pulmonary artery in Ayerza's disease, whereas in the other disease syphilis has been excluded and another single common etiologic factor has not been found. Primary sclerosis of the pulmonary artery and its branches has been described by Eppinger and Wagner, Posselt, Schutte, Miller, Liebig, Meyer and Lowenstein. The notable clinical features of this condition have been cyanosis, hypertrophy of the right ventricle, small left auricle, absence of evidence of passive hyperemia of the lungs and disproportion between the cyanosis and dyspnea. The disease is one of early life or early middle age. Death usually results from cardiac decompensation. The pulmonary arteries show more or less marked atherosclerosis, while the arterioles show usually a high degree of stenosing fibrosis. In Ayerza's dis-

ease the clinical symptoms are similar, but more marked, and include polycythemia, marked cyanosis, with hypertrophy and dilatation of the right heart. Attacks of intense dyspnea occur, giving rise to the clinical appellation of "cardiacos negros." This disease was first described in South America by Ayerza in 1901, and later by Arrillaga, and Escudero. The first American case was reported by Warthin in 1919. In these cases syphilitic sclerosis of the pulmonary artery and branches was the primary underlying pathology. While Warthin's case showed a syphilis of the pulmonary arterial system, he also states that a similar clinical picture might be brought by chronic pulmonary vascular disease due to other etiological factors than syphilis. The case reported by Bacon and Apfelbach presented the picture of chronic cyanosis for four years with hypertrophy of the right ventricle. The cyanosis was never as severe as in Ayerza's disease. The case, that of a woman, forty years of age, had been regarded as one of mitral stenosis. There was no emphysema, the left auricle was not enlarged. The development of the disease was insidious, following a severe pulmonary infection at the age of 32. There was no congenital heart disease. In the earlier stages of the disease there was a mild secondary anemia, in the later stages a polycythemia of six million red cells. Evidence of myocardial in-

sufficiency did not become conspicuous until eight months before death. Edema of the subcutaneous tissues appeared at that time. The autopsy showed: sclerosis of the pulmonary artery and branches; hypertrophy of wall of right ventricle; edema of myocardium; fibrous obliteration of pericardial sac; marked general hyperemia; slight ascites; edema of retroperitoneal tissues, gastro-hepatic ligament and wall of gall bladder; indurative shortening of the mesentery and mesocolon; moderate emaciation; slight generalized jaundice; cyanotic atrophy of the liver; atrophic emphysema of lungs; apical scars; localized bilateral fibroid pleuritis; localized perisplenitis and perihepatitis; moderate atherosclerosis of aorta; slight anthracosis of lungs and bronchial nodes; slight canities; ovarian cysts; bilateral hydrosalpinx; corset liver. Microscopically the changes in the pulmonary arteries were those of an intimal and subintimal fibrosis constricting the lumen, more marked in the case of the arterioles than in the larger arteries. Organized thrombi were found in some of the vessels. No evidences of syphilis were seen. There were no round-cell infiltrations in the vessel walls or around them. The authors regard this case as corresponding clinically with those described by Posselt and Eppinger. The cyanosis was never as marked as in Ayerza's disease and there was no marked enlargement of the spleen. Polycythemia was of a moderate degree. The possible etiologic factor in this case was the attack of influenza and pneumonia at the age of thirty-two. The authors conclude with the statement that they believe this case to be typical of pri-

mary sclerosis of the pulmonary artery, which they differentiate from Ayerza's disease.

*Pruritus Ani and Pruritus Vulvae of Fungal Origin.* By ALDO CASTELLANI (New Orleans Medical and Surgical Journal, March, 1927, p. 625).

Pruritus ani and vulvae are two of the most annoying and obstinate conditions with which the general practitioner comes into contact, and his therapeutic attempts are usually unsuccessful. That some of the forms of this affection are fungal in origin is not generally known, as there is no description of it given in the textbooks, although this form was described by Castellani as a separate entity some years ago. The patient complains of a very severe pruritus, not as a rule continuous, but at intervals. It is often worse at night, but attacks of unbearable itching may come on at any time. The inspection of the affected region in recent cases may reveal nothing at all, except signs of scratching; but in most cases on careful examination, minute red, slightly raised, infiltrated patches may be seen in the perianal region, occasionally arranged into two curved lines. In a number of old cases signs of dry or moist eczematous dermatitis are present, and streptococcus and other secondary bacterial infections may become engrafted on the mycotic condition. In some old-standing cases the skin is thickened, lichenified, and even presents the picture of the old so-called eczema ani chronicum. When the secondary bacterial infection becomes very heavy, especially if many colon and proteus bacilli are present,



the fungus may disappear or become extremely scarce. Illustrative cases are given. The cause has generally been found to be the presence of fungi of the genus *Epidermophyton*, the same fungi that produce ordinary tinea cruris, dhobie itch, tinea inguinalis, epidermophytosis inguinalis and pruritus interdigitalis pedum. Occasionally fungi of the genus *trichophyton* may be present. The species of epidermophyton found have been *E. cruris* and *E. rubrum*. Yeast-like fungi are also often present but it is doubtful if these play any important etiological role. The characteristics of these organisms are then described in full. The diagnosis depends upon the demonstration of the presence of the organism, either microscopically or culturally. A diagnosis of probability can often be made on clinical grounds alone, from the presence of the minute, red infiltrated patches, especially if the patient has a mycotic dermatitis of the toes, or gives a history of having suffered from dhobie itch or tinea cruris in the past. When a rich bacterial culture is also present it may be very difficult or impossible to isolate the fungus. The course of the condition is chronic, but periods of great improvement and apparent cure may alternate with periods of severe recrudescence. In certain very highly strung, nervous patients the pruritus may continue after the disappearance of the fungus. Very difficult are the cases of true eczema in which a secondary infection with the epidermophyton fungus has occurred. The diagnosis can usually be made by the microscopic examination of scrapings from the affected surface, macerated on a slide, in a 3 per cent solution of

potassium hydroxide. The preparation should be carefully covered with a cover glass, and examined with a medium high power. Fragments of mycelia and spore-like bodies will determine the diagnosis. Castellani has found an ointment of sulphur. praec. gr. 30, acid salicyl. gr. 30, vaseline 1 oz., very efficacious. Also Deek's ointment, salicyl. acid 4 parts, bismuth subnit. 10 parts, mercury salicylate 4 parts, oil of eucalyptus 4 parts, with vaseline and lanoline to make 100 parts, frequently works very well. Diluted tincture of iodine is at times useful; also a strong lotion of potassium permanganate (15 gr. to 1 dr., to 1 oz. distilled water). Frequent swabbing of the ano-perianal region with a perchloride of mercury lotion (1:1000) or a resorcin lotion (1-5 per cent) may be used. When the pruritus is unbearable painting the parts with a lotion of arg. nitro. 15 gr., spir. aether. nitr. 1 oz. may stop the itching at once, or after a short period of intensification. Treatment of the vulvar pruritus is essentially along the same lines.

*A Study of the Accessory Pancreas, With Report of One Causing Pyloric Stenosis.* By KELLEY HALE (Annals of Surgery, June, 1926).

The literature of accessory pancreas up to date is analyzed and a new case reported. This is of clinical importance in that it was associated with pyloric stenosis in an infant six weeks old, dying from hemorrhage after operation. The author comments on his case, as follows: An aberrant pancreas was found 4 mm. from the lumen of the pylorus with no evidence of ducts. The pathological and clinical

findings conformed in every detail with those of congenital pyloric stenosis. Many writers agree that pancreatic secretion can produce chemical irritation. The writer believes that the activity of the cells of the aberrant pancreas described before irritated the musculature of the pylorus in this infant to such an extent as to produce pathological changes. He does not think that congenital pyloric stenosis is the result of spasm; but like most functional disturbances will probably show a direct underlying cause, and he regards the aberrant pancreas in his case as the cause. He does not believe that the occurrence of aberrant pancreas and typical pyloric stenosis is purely coincidental, and would suggest that any pylorus removed at autopsy showing congenital stenosis should be cut in serial sections to see if this assumption is correct.

*Pneumococcus Meningitis and Endocarditis. Report of Twenty Cases of Pneumococcus Meningitis, With and Without Pneumococcus Endocarditis. Consideration of Treatment and Review of Literature.* By H. I. GOLDSTEIN and H. Z. GOLDSTEIN (International Clinics, Vol, III, Series 37).

Pneumococcus meningitis is not very common, but occurs sufficiently frequently to make it a subject of importance for discussion. Until recently the diagnosis of pneumococcus meningitis was regarded as a death warrant, but during recent years a number of recoveries have been reported, following various lines of treatment. A review of the literature of the subject is given. The authors report cases of

their own observation. As a result of their extensive study and analysis of the subject they present the following conclusions. It appears from the study of the literature and the results of various methods of treatment, that the early repeated spinal and cisternal lavage and drainage, the injection intraspinally and intracisternally of serum or antibody solution and the joint use of ethylhydrocuprein hydrochloride injections offer the best chance of saving the patients suffering from pneumococcus meningitis. Those cases failing to show improvement should have intraventricular injections and lavage through the fontanelle or trephine opening; and possibly also intravenous and intracisternal injections of ethylhydrocuprein solution, mercurochrome—220, neutral acriflavine or metaphen. It is possible with early diagnosis and prompt and active treatment to save some cases of pneumococcus meningitis. Early drainage, and even continuous drainage, will probably give the best results. There are on record in the literature about 150 cases of recovery from proved pneumococcus meningitis.

*Gastric and Duodenal Ulcer.* By A. WINKELSTEIN (Arch. Int. Med., 1926, 37, p. 541).

The study of gastric and duodenal ulcer shows that superficial erosions and ulceration of gastric and duodenal mucosa result from a great variety of causes, local and general, but that these tend to heal perfectly in the majority of individuals. In a certain number, however, healing is delayed or does not take place, and the lesion progresses and finally shows the characteristics of

a chronic peptic ulcer. It is this particular feature that constitutes the essential disease entity of peptic ulcer. The problem of gastric and duodenal ulcer becomes, therefore, centralized about this phenomenon of delayed or inhibited process of repair. Numerous theories have been offered in explanation. The commonly accepted opinion that local conditions are responsible for the interference with the normal process of healing seems inadequate. Other theories suggest some general bodily condition interfering with the normal physiologic course of healing, or that such inhibition of healing may be due to an excessive response to stimuli on the part of nerves and tissues, either locally or generally. Tetany, related conditions, disturbance of the vegetative nervous system, or a combination of these factors have been adduced in explanation of this hypothetical over-excitability. When patients with

gastric or duodenal ulcer, or with gastric neuroses, were tested, with controls, by various stimuli it was found that practically all ulcer patients respond excessively to mechanical, electrical and pharmacologic stimulation. Patients with gastric neurosis react in the same way, except to mechanical stimuli. They present, however, a marked contrast to the ulcer group in that they present well-defined stigmata of an abnormal vegetative nervous system. Winkelstein believes that this may prove to be of use clinically in differentiating the two conditions. Even after a surgical cure the over-excitability of the ulcer patient persists and this may be interpreted as indicating that it is the result of a constitutional factor, and not due to the presence of the ulcer. This paper may be taken as evidence of the rapidly growing view that peptic ulcer has a constitutional foundation.

## Reviews

*Modern Medicine. Its Theory and Practice.*

In Original Contributions by American and Foreign Authors. Edited by SIR WILLIAM OSLER, Bart., M.D., F.R.S., Late Regius Professor of Medicine in Oxford University, England; Honorary Professor of Medicine in the Johns Hopkins University, Baltimore; Formerly Professor of Clinical Medicine in the University of Pennsylvania, Philadelphia, and of the Institute of Medicine in McGill University, Montreal, Canada. Third Edition, Thoroughly Revised. Re-edited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia; Fellow of the Royal College of Physicians, London; Formerly Associate Professor of Medicine, the Johns Hopkins University. Assisted by Elmer H. Funk, M.D., Assistant Professor of Medicine, Jefferson Medical College Philadelphia. Volume IV, Diseases of the Respiratory System—Diseases of the Circulatory System. Pages 1011, Figures 104. Lea and Febiger, Philadelphia, 1927. Price in cloth, \$9.00.

Volume IV of the revised third edition of this well-known standard work of reference in internal medicine opens with a chapter on the Physiology of Respiration by G. W. Norris and T. M. McMillan. This is a new article replacing the one by Brown in the second edition, and represents a re-working of the old chapter, especially with reference to the physiology of respiration according to Haldane's views. The more recent work of Gesell on the respiratory mechanism is not mentioned. Chapter II treats of the Diseases of the Nasopharynx, Pharynx and Tonsils, and is written by Francis R. Packard. With the exception of two new paragraphs on Vincent's Angina and the so-called Agranulocytic Angina, the material in this chapter remains practically the same as in

the old edition, and cannot be said to have been fully brought up to date. Chapter III is by H. S. Birkett on Diseases of the Larynx; and its material is practically identical with that in the old except for the introduction of a paragraph on the use of heliotherapy and ultra-violet irradiation in the treatment of laryngeal tuberculosis. Chapter IV is on Hypersensitiveness of the Respiratory Tract, Hay Fever and Asthma, by Francis M. Rackemann. This is practically composed of new material and is an adequate discussion of the subject according to modern conceptions of these conditions. It is one of the best written chapters in this volume of the new edition, and is a sane discussion of the complex questions involved. Chapter V, on Diseases of the Bronchi, by Alexander McPhedran has been in part rearranged and new matter added, chief of which are the effects of war gases on the bronchi and Castellani's views and classification of hemorrhagic bronchitis. Inasmuch as the latter conditions are more or less rare, and their etiological foundation not in all cases secure, it might have been more useful to have given this space to some of the more important things omitted, as for instance, the X-ray findings in cases of foreign bodies in the bronchi. Chapter VI by H. A. Hare remains practically the same as in the old edition. Very little new matter has been added, and almost the only changes are in the omission of a small amount of unimportant material and some word changes. This section has not been brought up to date. The paragraph on Pneumoconiosis has been replaced by a more modern article on the subject by H. R. M. Landis, constituting Chapter VII. This is well written and adequate. Chapter VIII, Diseases of the Pleura, by F. T. Lord, also remains practically the same material as in the old edition, the new material added

being chiefly concerned with the differential diagnosis of subdiaphragmatic abscess. The next chapter, also by Lord, on Pneumotherapy has been increased by some new material on differential diagnosis. Chapter X, on Diseases of the Mediastinum, by H. A. Christian has some new matter included. Chapter XI, Diseases of the Diaphragm, by H. R. M. Landis, is wholly new material. Part II deals with the Circulatory System. Chapter XII, General Considerations in Cardiovascular Disease, by C. F. Hoover, has been recast and condensed. Diseases of the Pericardium are discussed by A. McPhedran in Chapter XIII. Very little has been added to the old material, and the section on tuberculous pericarditis has been omitted. With the exception of a paragraph on Quinidine Therapy, T. Lewis's Chapter XIV, on the Rate and Mechanism of the Heart Beat, remains practically as in the old edition. Chapter XV, Diseases of the Myocardium, by R. H. Babcock, has been much improved by having been brought up to date in its clinical portions, but from the standpoint of the pathology of the myocardium is lacking both in material and the proper interpretation of certain clinical conditions. Chapter XVI, Acute Endocarditis, by James B. Herrick, is new matter and presents this subject adequately and sanely. It is a good practical presentation of the essential clinical facts. Chapters XVII, XVIII and XIX, on Hypertrophy, Insufficiency and Dilatation, and Valvular Diseases have been rewritten by A. G. Gibson. These chapters are written from a modern standpoint, and are excellent. Gibson is one of the few writers on the heart who appears to recognize the important role played by syphilis in the production of cardiac and arterial disease. Chapter XX, Functional Disease of the Heart, by C. F. Hoover, is also an excellent treatment of this difficult subject. Chapter XXI, consisting of 200 pages on Congenital Cardiac Disease, by Maude E. Abbott, is a masterly article, and covers this ground more fully than any other previously published work upon this subject. It alone is worth the price of the volume, if such a mercenary view be permissible. It is par-

ticularly complete in its anatomical details and in the clinical picture of each form of congenital heart lesion. If anything is lacking in making this a wholly complete treatment of the subject it is in the discussion of the etiology and pathogenesis of congenital cardiac lesions. As a matter of fact we have little positive knowledge of these, and it is very likely that Dr. Abbott has given us all of importance that is really known about these subjects. Chapter XXII, Diseases of the Arteries, and Chapter XXIII, Aneurism, are by C. P. Howard. The subjects are covered adequately, particularly the last one. The volume closes with Chapter XXIV, Thrombosis, Embolism and Phlebitis, by G. Blumer, and Chapter XXV, Diseases of the Lymphatic Vessels, by A. S. Warthin. Both of these chapters have been brought up to date by the insertion of new material. Altogether the volume is very satisfactory and contains much valuable material not available in a compact form elsewhere. It is inevitable in a work of this kind that the discussion of any given subject must lag somewhat behind the current medical writings of the present time. For this reason writers of articles omitting discussion of the most recent work may appear to be negligent in not bringing their articles up to the minute. On the other hand, the greater part of current writings on medical research are only of transient significance, even though they be highly advertised. Much safer is the textbook article that is built up on researches that have weathered the test of time and experience. The Osler Modern Medicine may be commended for the safe conservatism of most of its articles.

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*Goiter and Other Diseases of the Thyroid Gland.* By ARNOLD S. JACKSON, M.D., Jackson Clinic, Madison, Wisconsin. 401 pages, 151 illustrations. Paul B. Hoeber, Ind., New York, 1926. Price in cloth, \$8.00.

In his introduction the author states his convictions as to the importance of goiter to the nation. One of the objects of his book is to break down the old theory that

the goiter of youth is merely a physiological enlargement of the thyroid gland which would in time spontaneously disappear. Jackson believes that many of the goiters now requiring surgical operation might have been cured had it not been for the too-prevalent acceptance of these misconceptions. He offers the following classification of goiter: colloid, adenomatous (simple or toxic) and exophthalmic. He believes that iodine should be administered as a preventive to all children between the ages of eight and twenty who live in the goiter belt. Iodine will not effect a cure in the presence of an adenomatous goiter regardless of its size; but if the patient is kept under close observation, it may be given in small amounts merely to retard the growth of the adenoma until the age of twenty-one. The use of iodine in the prevention of goiter after this age is contraindicated because it is no longer of value as a preventive; it has no permanent effect in the treatment of colloid goiter, and iodine hyperthyroidism may easily be induced. The one exception to the rule that iodine should not be administered to adults is found in the treatment of exophthalmic goiter before and after operation. The diagnosis in these cases must be clearly established before the use of iodine is justified. The prevention and treatment of colloid goiter is a purely medical problem and involves a comprehensive system of organization throughout the goiter area. Adenomatous goiters should be considered as potential sources of hypertension, nephritis, myocarditis and malignancy, and as such should receive early surgical treatment. Exophthalmic goiter is a surgical disease, and for its successful treatment requires the close cooperation of the internist with the surgeon. There are twenty-one chapters in this monograph, dealing respectively with the normal thyroid and its functions, the history, geographical distribution, etiology, classification, symptomatology, diagnosis and treatment of goiter, thyroiditis, myxedema, cretinism, metabolic rate, use of iodine, the heart in toxic goiter, surgical treatment, surgical complications and mortality factors. These subjects are very thoroughly presented. The book is well printed; the il-

lustrations are numerous and of fair quality, but some of them are not convincing. In Fig. 97 a hyperplastic germinal center of a lymph node is labelled lymphosarcoma. The pathology is borrowed largely from McCarty. There is apparently no conception of any constitutional basis for the conditions of exophthalmic goiter and toxic adenoma. The relationship of these to the thymico-lymphatic constitution is not considered. The prevailing medical and surgical conceptions of these diseases are accepted by the author and nothing new of any importance is added. He is clinically sound on all points relating to the use and abuse of iodine, and his emphasis of these constitutes the chief service of this book.

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*Approaching Motherhood.* Question and Answers of Maternity. By GEORGE L. BRODHEAD, M.D., Consulting Obstetrician, Bellevue and Allied Hospitals, Harlem Division; Visiting Obstetrician, Knickerbocker Hospital, New York. Third Edition. 193 pages. Paul B. Hoeber, Inc., New York, 1927. Price in cloth, \$1.50.

The previous edition was reviewed in these columns, and the reviewer can only repeat here what was said before as to the practical value of this little volume. It is a clear and simple answer to the questions of the expectant mother, telling her not only what she should know, but explaining also the fallacy of many popular beliefs. Opportunity has been taken by the author to make a few minor corrections in this edition.

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*Disorders of the Nose, Throat and Ear.* Problems of Deafness. By AARON ROTH, M.D., F.A.C.S., Attending Ear and Throat Surgeon, Jewish Hospital, Brooklyn. Assistant Chief of Staff, Ear, Nose and Throat Department, Brownsville, E. N. Y. Hospital, Brooklyn. 238 pages, 29 original illustrations by the author. Physicians and Surgeons Book Company, Brooklyn, New York, 1927. Price, \$2.50.

This little treatise was primarily designed for the layman and the educator interested in the subjects discussed, but in the belief that it would also prove profitable to the

medical student as auxiliary reading and to nurses and general assistants associated with the specialty of otolaryngology. It aims to present the essential facts pertaining to the mechanism of the organs of smell, voice and hearing; and to point out the general functions of these structures under normal and abnormal conditions, and to indicate some of the natural processes of healing and scientific principles of prevention and repair. It is a condensed manual of the ground it aims to cover. It is non-technical and in the popular science form, and is illustrated by simple original drawings. A survey of the material shows much useful information expressed in a simple form. There are many evidences of good common-sense views, and the reviewer noted no signs of any effort to promote any especial fad of treatment. Too elementary for a medical student or practitioner, the simple presentation offered here of the most important facts of this specialty should be of service to nurses.

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*Tobacco and Physical Efficiency.* A Digest of Clinical Data (With Annotated Bibliography.) By PIERRE SCHRUMPF-PIERON, M.D., Professor of Clinical Medicine, University of Cairo. Published under the Auspices of The Committee to Study the Tobacco Problem. 134 pages. Paul B.

Hoeber, Inc., New York, 1927. Price in cloth, \$1.85.

The Committee to Study the Tobacco Problem offers this volume not as an expression of any opinion of its own on the effects of tobacco on the animal organisms, but as a concise review of many opinions, often conflicting, of many authors. The review of the foreign literature has been made by Dr. E. L. Fisk. Seven hundred and fifty bibliographic references give evidence of the thoroughness of the attempt to present all of the data concerning the effects of the use of tobacco. The facts concerning these effects have not been easy to get at; and this book attempts to present an unbiased and truthful summary of all the scientific work that has been done in this line. Because of the active propaganda for and against the use of tobacco and with its constantly increasing use it is desirable that the subject be thoroughly investigated and seriously discussed. In this volume are presented the known facts giving a definite foundation on which to base opinions and arguments. The physician will find here the data that will enable him to answer questions continually addressed to him as to the good or evil effects of the use of tobacco. They are given here from a purely scientific standpoint wholly free from prejudice or exaggeration.

## College News Notes

"On August 22, 1927, P. M. Ashburn, Colonel, Medical Corps, U. S. Army, assumed the appointment as Librarian of the Army Medical Library at Washington, D. C. Since 1923, Colonel Ashburn had acted as Professor of Military Hygiene at the United States Military Academy at West Point. Colonel Ashburn was relieved at West Point by Colonel M. A. W. Shockley who was transferred from his command of Beaumont General Hospital, El Paso, Texas. Lieutenant Colonel James M. Phalen, formerly Librarian of the Army Medical School, has gone to Panama as Department Surgeon. Both Lieutenant Colonel Phalen and Colonel Ashburn are Fellows of the College."

### Obituaries

Dr. Thomas Davies Coleman, Augusta, Georgia—August 2, 1927. Elected a Fellow of The College January 1, 1921.

Dr. H. Edwin Lewis, New York, New York—August 6, 1927. Elected a Fellow of The College February 20, 1921.

Dr. Ignatz Morvay Rottenberg, New York, New York—August 9, 1927. Carcinoma of the Stomach. Elected a Fellow of The College June 25, 1915.

Dr. Robert Stevenson, Stoney Brook, New York—August 22, 1927. Elected a Fellow of The College December 30, 1926.

Dr. Robert Wernigk died at his home in Los Angeles on the 26th of August, 1927, soon after returning from Nauheim where he had been seeking health. Dr. Wernigk was born in Illinois in 1861 of Bavarian parentage. His father was a physician, as was his grandfather. His great-grandfather was a surgeon in Napoleon's Army. Dr. Wernigk received his medical education at Rush, graduating in 1882. He practiced medicine in Los Angeles for forty years. He was an able physician. His medical judgment and his willingness and his knowledge of the needs of his patients were highly developed. He enjoyed a very large practice and his patients loved him. He made frequent trips to medical centers in America and Europe. During the War, Dr. Wernigk gave much time and strength as a member of the Medical Advisory Board of Southern California. He belonged to the Medical Association of his County and his State; to the American Medical Association, and was a Fellow of The American College of Physicians.





# Insulin and Carbohydrate Tolerance\*

WILLIAM M. BRACE, A.B., M.D., *Ann Arbor, Mich.*

## INTRODUCTION

SINCE the discovery of insulin by Banting (1), there has been a great deal written concerning the cure of diabetes mellitus with this new therapeutic agent. MacCallum (2), Boyd and Robinson (3) have given us some meagre hope of a cure with microscopical evidence in favor of the regeneration of the islands of Langerhans; while Newburgh (4), Harrison (5), and others (6, 7) present clinical evidence of a negative nature concerning a cure. With this controversy still unsettled, five cases were carefully selected from our diabetic clinic with this question ever present. Is there any evidence of a cure, or even a partial cure of human diabetes mellitus as shown by the tolerance for glucose after insulin has been used daily over a long period of time?

## METHOD OF PROCEDURE

The high fat, low protein, low carbohydrate weighed diets of Newburgh (8) and Marsh were used throughout, and the insulin was adjusted to keep the urine just free from any reducing substance and ketone bodies. The ob-

servations reported later in this paper were made on five patients who had been receiving insulin daily, and had been observed at different intervals at the clinic over long periods of time, varying from 32 to 45 months. Observations on these five patients provide data as to whether or not insulin improves the tolerance for glucose of each patient, when the treatment is prolonged over many months. By tolerance for glucose is meant the total glucose content of a diet that a patient can take without glycosuria. The total glucose content of any diet is derived by the formula: 100% of the carbohydrate plus 58% of the protein plus 10% of the fat (9). The blood sugar estimations were made by the Folin and Wu method. Benedict's quantitative and qualitative methods have been used for sugar. Gerhardt's ferric chloride test for diacetic acid, and the nitroprusside test for acetone in the urine. The patients were weighed, when possible, to the nearest kilogram without clothes. If weighed with clothes, due allowance was noted and made.

For insulin injection one cubic centimeter syringes, which were calibrated in twentieths or hundredths of a cubic centimeter, were used. Dosage is recorded throughout as so many units. The drug was administered subdermally two or three times a day. Insulin

\*From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan; aided in part by the Frederick Stearns Fellowship, Detroit, Michigan.

was given routinely, unless otherwise specified, at 7 A. M.; 11:30 A. M., and 5 P. M. each day.

Five patients have been kept under observation for periods of 32 to 45 months, each on a diabetic diet suitable for that particular individual and with enough insulin each day to keep the urine aglycosuric and aketonuric. Upon their initial visit each patient was studied at length in the hospital, at which time their glucose tolerance was determined. Each has been restudied in the hospital as well as during other subsequent visits to the Diabetic Out-Patient clinic, at which time glucose tolerance redeterminations were made.

These five patients form a small group, who have distinguished themselves for their loyalty, honesty, intelligence and long period of observation. They were accordingly selected for this study because we were justified in believing that we would get reliable information from them. At the beginning of the investigation, which was undertaken some two years ago, it was not known whether the subsequent treatment with insulin would give evidence of improvement or the converse. As already mentioned, these five cases are used because of their reliability and because they have continued to adhere strictly to our plan to the end of our study. The glucose tolerance of each individual is always determined by beginning with bed rest and a daily diet consisting of protein 20 grams, fat 86 grams, and carbohydrate 15 grams, without insulin. The total glucose content of this diet is 30 grams. After an aglycosuric period of three to four days, each

foodstuff is proportionately increased so that the next diet has a total glucose content of 50 grams and consists of protein 28 grams, fat 129 grams, and carbohydrate 20 grams. Similarly, after aglycosuric periods of the same time length, the diet is raised proportionately until its total glucose content is 70 grams, consisting of protein 34 grams, fat 163 grams, carbohydrate 29 grams. The fourth level affords 90 grams of total glucose, consisting of protein 54 grams, fat 210 grams, and carbohydrate 37 grams. To the latter diet carbohydrate is added in ten gram measures every third or fourth day, until there is a glycosuria.

It will be found that at a certain place in this plan each diabetic will have glycosuria. Any part of this regime that he is able to use just without glycosuria measures his complete ability to burn glucose, (a pancreatic function), or his glucose tolerance. This point in the dietary scheme in moderately severe, or severe diabetics is usually so low in calories that the patient would have to live on a sub-maintenance diet. Of course, this is a definite indication for a proportionate increase in the amount of each of the foodstuffs to make up a maintenance diet for that particular individual. Since glycosuria would occur with additional food, insulin in proportionate doses to keep the urine aglycosuric and yet prevent hypoglycemic reactions is given. This has been the procedure in each of the five cases.

#### *Report of Cases*

*Case I.* L. C., schoolgirl, age 18, first complained of polyuria, polydipsia, polyphagia, in June, 1922. She entered the hos-

pital in September of the same year, weighing 37 kilograms. The urine gave strongly positive tests for glucose and diacetic acid, and a fasting blood sugar was 0.38%. It was found that she could tolerate without insulin and just without glycosuria a diet of protein 54 grams, fat 214 grams, and carbohydrate 38 grams, which has a total glucose content of 90 grams. This amount was her original glucose tolerance.

In January, 1923, she returned to the clinic because of infection and uncontrollable glycosuria. After both had entirely disappeared, it was found that now she could only tolerate without insulin, a diet composed of protein 31 grams, fat 176 grams, and carbohydrate 28 grams, which contained 61 grams of glucose, the new level of glucose tolerance. Weight at this time was 39.1 kilograms.

In May, 1923, because of uncontrollable glycosuria of unknown cause, she returned to the clinic, weighing 34.9 kilograms and with the next succeeding twenty-four hour urine specimen containing 5.3 grams of glucose. After aglycosuria was established it was noted that now a diet of protein 28 grams, fat 129 grams, and carbohydrate 20 grams, with a total glucose content of 46 grams could be tolerated without insulin and glycosuria. It was found that this diet contained insufficient calories (1368) for an active girl of her age. Insulin and a maintenance diet of protein 55 grams, fat 220 grams, and carbohydrate 35 grams were prescribed in June, 1923. At first a daily total of 9(5-4) units of insulin in divided doses were required to keep her urine aglycosuric.

Because of infection, coryza, and tonsillitis, she returned to the clinic October, 1923. She was discharged in December of the same year, with a diet of protein 55 grams, fat 220 grams and carbohydrate 40 grams, and with a total of 59 (22-14-23) units of insulin in divided doses during the day. Weight then was 42.5 kilo.

This patient next revisited the clinic January 1st, 1926, because of glycosuria, hypoglycemic reactions and head cold. The next twenty-four hour urine specimen contained 34.4 grams of glucose and a fasting blood

sugar was .222%. After aglycosuria had been established, it was found that she could tolerate a diet of protein 55 grams, fat 220 grams and carbohydrate 35 grams, with a daily dose of 56 units of insulin. It was found that by spacing the insulin dosage differently, that is, 32 units at 7 A.M., 20 at 5 P.M., and 4 at 10 P.M., the urine would remain aglycosuric at all times. Discharge weight was 54.5 kilos. She has been aglycosuric and without insulin reactions on this regime for the past four months.

*Case II.* R. B., contractor, age 28, first noted increased thirst and urination with loss of weight in February, 1922. He entered the clinic October, 1922, with a weight of 53.9 kilos and a urine, which gave strongly positive tests for glucose and diacetic acid. It was found that he could tolerate, without insulin and just without glycosuria, a diet composed of protein 40 grams, fat 180 grams, and carbohydrate 30 grams. This diet contained a total glucose of 71 grams or the original glucose tolerance.

In February, 1923, the patient returned because of uncontrollable, irregular glycosuria and infection, head cold. After the urine was rendered aglycosuric it was found that he could not tolerate, without glycosuria, a diet with a total glucose content of 64 grams composed of protein 33 grams, fat 171 grams, carbohydrate 28 grams. Thus the glucose tolerance at this time lies somewhere between 64 and 50 grams of glucose, the latter being in the next lower routine diabetic diet of protein 28 grams, fat 129 grams, and carbohydrate 20 grams. Because of the glycosuria and of the patient's occupation, age, sex, and height, (6 feet, 2 inches) it was readily observed that a maintenance diet with insulin would be necessary.

Accordingly, in March, 1923, a diet of protein 58 grams, fat 281 grams, carbohydrate 57 grams, with a daily total of 28 (14-0-14) units of insulin in divided doses during the day were prescribed to keep the urine aglycosuric. Weight was then 53 kilos. Because of a head cold the insulin dosage was raised after one month to a total of 36 (18-0-18) units in divided doses during the day. The diet was kept constant. From

May, 1923, to January, 1925, the patient was aglycosuric and free from hypoglycemic reactions on the above diet and 36 units of insulin daily.

In January, 1925, he contracted influenza and upon recovery it was found that now 48 (8-20-20) units of insulin in divided doses during the day, together with the same diet, were needed in order to maintain aglycosuria. From the latter part of January, 1925, to January, 1926, this regime was continued without glycosuria or hypoglycemic reactions. Average weight during this period was 65.9 kilograms.

In the latter part of January, 1926, this patient entered the hospital semi-comatose due to a severe upper respiratory infection. After aglycosuria had been established and the infection had been entirely cleared, he was discharged in March, 1926, on a diet of protein 60 grams, fat 280 grams and carbohydrate 60 grams, with a total of 85 (25-30-30) units of insulin in divided doses. Weight was upon discharge 60 kilograms.

*Case III.* R. K., telephone operator, age 18, first noticed dysuria, pruritus vulvae, loss of weight and strength, polyuria and polydipsia in January, 1924. She entered the clinic February, 1924, weighing 46.1 kilograms, with strongly positive urinary glucose and diacetic acid tests. After aglycosuria had been established, it was found that this patient could tolerate without glycosuria a diet of protein 55 grams, fat 225 grams, and carbohydrate 35 grams. This diet has a total glucose content of approximately 90 grams, which is the original glucose tolerance.

As it was decided in April, 1924, to increase the diet slightly and add insulin, this patient was given a single dose of 8 units at noon with a diet of protein 55 grams, fat 230 grams, and carbohydrate 45 grams.

During the interval between hospital visits the patient found that it was necessary, because of an irregular glycosuria, to raise the insulin to a single dose of 20 units at noon. The diet remained constant.

As this regime did not keep her aglycosuric, she returned to the clinic October, 1924, with a weight of 53 kilograms, and

the urine yielding 27.1 grams of glucose in the next 24 hours. After the urine was aglycosuric, and the foodstuffs raised gradually and proportionately, it was found that she could now only tolerate without insulin and glycosuria, a diet composed of protein 34 grams, fat 164 grams, and carbohydrate 30 grams. The glucose content of this diet is approximately 70 grams, the new glucose tolerance level. The patient was discharged on the same diet of protein 55 grams, fat 230 grams, and carbohydrate 45 grams, but with a daily total of 30 (10-10-10) units of insulin in divided doses during the day.

This kept her aglycosuric and free from hyperinsulinemia reactions and infections until March, 1926. She then returned with a nasopharyngitis and uncontrollable glycosuria. At this visit a fasting blood sugar was .222% and the urine gave strongly positive tests for glucose and diacetic acid. The weight was 61 kilograms.

After the infection had been cleared and the urine rendered aglycosuric, she was discharged on exactly the same regime. On this plan she has remained both aglycosuric and free from hypoglycemic reactions to date.

*Case IV.* D. A. H., dietitian, age 25, first noted the symptoms of loss of weight, weakness, polyuria and polyphagia in August, 1923. At the time of entrance to the clinic, August, 1923, she weighed 45 kilograms and the urine showed strongly positive tests for glucose and diacetic acid. It was found that she could tolerate, without insulin and glycosuria, a diet of protein 54 grams, fat 210 grams, carbohydrate 37 grams, plus 30 extra grams of carbohydrate. This diet has a total glucose content of 120 grams and a caloric value of 2374 calories. Because of the patient's under-nutrition, weakness, and the insufficient caloric value of the tolerated diet, she was given in November, 1923, a diet of protein 55 grams, fat 250 grams and carbohydrate 70 grams, with a daily total of 52 (32-20) units of insulin in divided doses. In the interval between clinic visits on this regime there was a history of an occasional slight glycosuria and a hypogly-

cemic reaction, but no infections of any nature.

In April, 1925, the patient returned to the clinic weighing 59 kilograms. At this time it was found that the aforementioned diet of protein 55 grams, fat 250 grams and carbohydrate 70 grams, combined with a daily total of 52 (32-20) units of insulin in divided doses kept the urine aglycosuric.

Because of a head cold the patient revisited the clinic in August, 1925, weighing 60 kilograms. At this visit it was found that in order to avoid glycosuria and insulin reactions, the diet must consist of protein 60 grams, fat 220 grams, and carbohydrate 60 grams, with the same daily total of 52 (32-20) units of insulin in divided doses. She returned home in April, 1926, weighing on this regime 63 kilograms. She has since remained free from glycosuria and insulin reactions.

*Case V.* F. J., age 26, junior medical student, first complained of weakness, polyphagia, polydipsia, polyuria, and loss of weight in January, 1919. He entered the clinic in June, 1919, weighing 45 kilograms and the urine giving strongly positive tests for glucose and diacetic acid. It was found that the patient could tolerate without insulin and glycosuria, a diet with a glucose content of 90 grams and composed of protein 53 grams, fat 210 grams and carbohydrate 37 grams.

Because of an infection (coryza) and a slight dietary indiscretion, the patient reentered the clinic in March, 1923, semicomatose, weighing 45 kilograms. After the infection had disappeared and the coma had been relieved, it was determined that he could still tolerate a diet with a total glucose content of 90 grams, composed of protein 53 grams, fat 210 grams, and carbohydrate 37 grams.

Because of undernutrition the patient was given, in March, 1923, a diet composed of protein 70 grams, fat 290 grams, and carbohydrate 75 grams, and a daily total of 26 (13-13) units of insulin in divided doses.

After five months of treatment with insulin, in August, 1923, it was found that he could continue to tolerate without glyco-

suria the same diet, which has a total glucose content of 90 grams. After an infection, coryza, in April, 1924, it was found necessary to take daily 46 units (16-15-15) of insulin in divided doses together with the same diet to remain aglycosuric.

In August, 1924, he found that with the same diet the daily insulin dosage could be reduced to 41 (21-10-10) units in divided doses, without a resulting glycosuria. It is believed that the reduction in dosage at this time was due to the slowness in the resolution of the infection (coryza) together with the increased muscular activity in the summer months. The diet remaining constant, the dosage was reduced to 40 (20-8-12) units daily in divided doses in December, 1924, without glycosuria. The same diet and insulin dosage were continued, and on December 31, 1924, a series of blood sugars were taken, with the following results:

TABLE I

Time	Insulin (units)	Blood Sugar %
7:00 A.M. (fasting)	..	.128
7:30 A.M.	20	...
8:00 A.M.	..	.153
11:30 A.M.	8	...
12:45 P.M.	..	.129
5:00 P.M.	12	...
6:00 P.M.	..	.073

In January, 1925, the diet was reduced to protein 66 grams, fat 255 grams, and carbohydrate 64 grams, with 42 (20-9-13) units of insulin per day. This dosage was reduced in June, 1925, to 34 (13-8-13) units daily, with the diet constant.

For the past one and one-half years the patient has been on this regime, aglycosuric and with only an occasional insulin reaction, which was induced by increased muscular activity such as tennis, swimming, canoeing, surveying on mountains.

In January, 1926, the patient, now a third year medical student, determined the amount of glucose in both his own and normal urines by the microscopical method of Shaffer and Hartman (10). Both the normal urines and his own, the diabetic, con-

tained from 400 to 900 milligrams of glucose per 24 hours.

In February, 1926, a fasting blood sugar was .136%. In August, 1926, because of hypoglycemic reactions after increased muscular activity, the daily dosage was reduced to 27 (13-5-9) units per day. The diet was unchanged. The patient now weighs 54.5 kilograms, takes the same diet and has reduced his dosage to 26 (12-5-9) units per day, without glycosuria.

### Discussion

Case I was observed for nine months with a diabetic diet only, and for forty-two months with both diet and insulin. This case shows a gradually decreasing tolerance with a uniform diet and without insulin over a nine-month period. The gradual decrease from an original glucose tolerance of 90 grams, to 61, then to 46 grams was due to infection.

ing of the insulin dosage, but more especially perhaps to the omission of 5 grams of carbohydrate from the diet, which had been uniform for the past three years. Instead of insulin at 7:00 and 11:00 A.M. and 5:00 P.M., it was found that aglycosuria was only constantly present with the administration of the drug at 7:00 A.M., 5:00 and 10:00 P.M. Any further lowering of insulin or different time of dose caused glycosuria.

Case II shows that with diabetic diet alone the glucose tolerance decreased within four months from the original level of 71 grams to a number of grams somewhere between 64 and 50. He had insulin and was observed for 45 months. During the last three years the diet has been constant except with the small variance of from one to three grams of each of the food

TABLE II

Case I. L. C.

Date	P. Gms.	Diet F. Gms.	CH Gms.	Total Glucose Gms.	Insulin Units	Urine Glucose
Nov., 1922	54	214	38	90	None	Neg.
Feb., 1923	31	176	28	61	None	Neg.
May, 1923	28	129	20	46	None	Neg.
June, 1923	55	220	35	88.9	9 (5-4)	Neg.
Dec., 1923	55	220	40	93.9	59 (22-14-23)	Neg.
Jan., 1926	55	220	35	88.9	56 (32-0-20-4)	Neg.

With a constant diet the dosage of the drug had to be increased from 9 to 59 units daily in two months time for the same reason—infection. On unchanged diet and dosage of insulin glycosuria and hypoglycemic reactions were avoided for 36 months. At the end of this period it was observed that three units of insulin could be omitted, so that the daily dose was 56 units. This was in part due to different spac-

stuffs. To avoid glycosuria in the beginning, 28 units of insulin were necessary. Because of various infections the dosage had to be increased from 28 units to 36, then 48 and finally 85 units, with a constant diabetic diet.

It is exceedingly interesting and instructive to note that during the insulin dosage there are two long periods of time, during which an unchanged diet and insulin dosage both avoided

hyperinsulinemia and glycosuria. The first period of 20 months was from May, 1923, to January, 1925. The second of 12 months was between January, 1925, and January, 1926. The diet was absolutely constant throughout both of these periods, but the insulin dosage varied, being 36 units daily for the first period and 48 units for the second.

of insulin and a constant diabetic diet. for six months, the glucose tolerance when redetermined was 70 grams. The patient was observed for 32 months with daily insulin. It should be noted that although the diet was kept constant throughout this entire period, the original daily amount of insulin had to be increased gradually from 8 to 20 units, then to 30 units daily in order

TABLE III

Case II. R. B.

Date	P. Gms.	Diet F. Gms.	CH Gms.	Total Glucose Gms.	Insulin Units	Urine Glucose
Nov., 1922	40	180	30	71	None	Neg.
	28	129	20	50	None	Neg.
Mar., 1923	33	171	28	64	None	4 plus
Mar., 1923	58	281	57	118.7	28 (14-0-14)	Neg.
Apr., 1923	58	281	57	118.7	36 (18-0-18)	Neg.
Jan., 1925	58	281	57	118.7	48 (8-20-20)	Neg.
Jan., 1926	60	280	60	122.8	85 (25-30-30)	Neg.

TABLE IV

Case III. R. K.

Date	P. Gms.	Diet F. Gms.	CH Gms.	Total Glucose Gms.	Insulin Units	Urine Glucose
Mar., 1924	55	225	35	90	None	Neg.
Apr., 1924	55	230	45	99.9	8 (0-8-0)	Neg.
June, 1924	55	230	45	99.9	20 (0-20-0)	Neg.
Oct., 1924	55	230	45	99.9	30 (10-10-10)	Neg.
Mar., 1926	55	230	45	99.9	30 (10-10-10)	Neg.

Infection, influenza, between these periods had reduced the tolerance. It must be observed that the high dosage of 85 units daily and the same diet was the final amount given. The increased dosage was needed after coma with an acute upper respiratory infection.

Case III presents the most important evidence of any one of the five cases. The original glucose tolerance level was 90 grams. After daily doses

to eliminate glycosuria. The cause of each increase in dosage was glycosuria with infection. It is of interest to note that the patient has remained without glycosuria and hypoglycemia from October, 1924, to date on a constant diet and constant daily dosage of insulin. Any reduction in insulin or increase in the diet causes glycosuria.

Case IV shows the same end results with a constant daily insulin dosage for 36 months, but with a varied diet.



The insulin dosage has been 52 (32-20) units per day. The first diet with insulin contained a total glucose content of 126.9 grams, while the second had 116.8 grams. Although the insulin dosage was constant throughout, ten grams of the total glucose had to be removed from the first diet in order to keep the patient free from glycosuria.

found to be still 90 grams. For 21 months the same diet and daily dosage of insulin as shown in Table VI were given. Any reduction of insulin resulted in glycosuria. To maintain aglycosuria during infection, insulin dosage had to be increased to 46 units. As the infection gradually cleared, he was only able to reduce his daily dose to 40 units, with the same diet. His

TABLE V

Case IV. D. A. H.

Date	P. Gms.	Diet F. Gms.	CH Gms.	Total Glucose Gms.	Insulin Units	Urine Glucose
Nov., 1923	54	210	67	120	None	Neg.
Nov., 1923	55	250	70	126.9	52 (32-0-20)	Neg.
Apr., 1925	55	250	70	126.9	52 (32-0-20)	Neg.
Aug., 1925	60	220	60	116.8	52 (32-0-20)	Neg.
Apr., 1926	60	220	60	116.8	52 (32-0-20)	Neg.

TABLE VI

Case V. F. J.

Date	P. Gms.	Diet F. Gms.	CH Gms.	Total Glucose Gms.	Insulin Units	Urine Glucose
July, 1919	53	210	37	90	None	Neg.
Mar., 1923	53	210	37	90	None	Neg.
Mar., 1923	70	290	75	144.6	26 (13-13)	Neg.
Apr., 1924	70	290	75	144.6	46 (16-15-15)	Neg.
Aug., 1924	70	290	75	144.6	41 (21-10-10)	Neg.
Dec., 1924	70	290	75	144.6	40 (20-8-12)	Neg.
Jan., 1925	66	255	64	127.7	42 (20-9-13)	Neg.
June, 1925	66	255	64	127.7	34 (13-8-13)	Neg.
Aug., 1925	66	255	64	127.7	27 (13-5-9)	Neg.
Jan., 1927	66	255	64	127.7	26 (12-5-9)	Neg.

Case V is perhaps by far the most interesting and instructive. On a diabetic diet without insulin for 9 months, the glucose tolerance was the same at the beginning as at the end of the period, namely, 90 grams. This case was observed for 45 months with daily insulin. After he had received a constant diet and daily dose of insulin for 5 months, the glucose tolerance was

tolerance is now clearly less than at the beginning. In January, 1927, he was able to reduce the daily dosage to the original amount used in March, 1923, namely 26 units. The total glucose of the diet of March, 1923, was 144.6 grams, while that of January, 1927, was 127.7 grams. Although the insulin dosage remained uniform in order to avoid glycosuria, the diet of

January, 1927, must contain 16.9 grams less of glucose than did the diet of March, 1923.

### CONCLUSIONS

To date there has been no evidence advanced which shows that the daily administration of insulin over long periods of time has been followed by a gain in the total glucose tolerance of a diabetic, which could not be explained by desugarization or recovery from infection.

A failure to obtain evidence of im-

provement in the tolerance for glucose in five patients, who had received weighed, high fat, low protein and low carbohydrate diets and daily insulin over periods varying from 32 to 45 months, has given us no ground for believing that insulin is capable of effecting a cure or a partial cure of human diabetes mellitus. Insulin has shown no more ability to arrest the downward progress of the disease than the earlier treatment without the drug. Each of these patients has lost tolerance during the period of treatment with insulin.

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# The Conservative Treatment of Gangrene Complicating Diabetes\*

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THE treatment of gangrene complicating diabetes is a problem not strictly medical or surgical, but one which calls for the closest cooperation between surgeon and internist.

Often the type of treatment instituted depends on the specialty of the doctor first consulted. The general practitioner often considers gangrene a surgical problem and the surgeon usually sees the patients in consultation. The laity speaks of gangrene and amputation in the same sentence.

If surgery is the only method of treatment considered, limbs which might have been saved by conservative measures are amputated. On the contrary, if the internist fails to seek surgical counsel, continuing conservative treatment when amputation is indicated, toxemia or death may ensue; in either instance, an injustice is done the patient.

This paper deals principally with the medical phase of this problem and the measures available for conservative treatment.

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**HISTORY:** Credit for the discovery of the relationship between glycosuria and gangrene probably should be given to Marchal (1) who, in 1852, presented a report to the Academy of Medicine in Paris. However, as early as 1806, Garco (2) pointed out that diabetics often suffered from ulcerations on the legs.

**ETIOLOGY:** There are many speculations relative to the cause of the vascular disease found in the majority of diabetic patients past middle age. Marchal (1) considered the possible effect of the long-continued hyperglycemia upon arteries. Joslin (3) has noted a positive Wassermann reaction in 11% of his diabetic patients suffering from gangrene, while the proportion was only 1.6% for 1,000 Wassermann tests in his series of diabetic patients. French writers (4, 5, 6) have also stressed the importance of syphilis as an etiological factor.

Letulle, Labbe, and Heitz (7) suggest that as a result of long-continued hypercholesterolemia, cholesterol may be retained in the intima of the arteries and thus promote calcification and obliteration of the lumens of the vessels. Their hypotheses are more or less confirmed by Labbe's (8) later report. He found a marked increase in the calcium content (10 times nor-

mal) in the sclerotic arterial walls of a diabetic sixty-two years of age. There was also a marked increase in the magnesium and cholesterol content. This patient's urine had shown sugar for eighteen years and he had symptoms of circulatory insufficiency in the legs for two years. Seven months prior to hospitalization, he developed an ulcer of the right fifth toe; four weeks prior to entry, two toes of the right foot had become black and very painful. The blood cholesterol was 2.50 on entrance (it fell to 1.85 eight days later, after the urine had become sugar free by the use of insulin). The blood calcium was .105 grams per litre. A month after entry, the right leg was amputated and the patient died a few hours later. The high blood cholesterol, followed by extension of the gangrene, and the death of this patient in a short time, confirms the ideas of Gray (9) in regard to the value of blood fat or cholesterol estimation in determining the prognosis in diabetes. Abnormal blood fat was found by this investigator in 78% of 1,062 specimens obtained from diabetic patients. He concluded from his tables that the higher the blood fat level (or cholesterol) the shorter the life expectancy.

The occurrence of vascular disease in Warren and Root's (10) series of cases was more closely related to the duration of the diabetes than to the patient's age at the time of onset of the symptoms.

Beard (11) has pointed out that exposure to cold may be a possible indirect cause of gangrene.

**PATHOLOGY:** The term "arteriosclerotic gangrene with diabetes"

as proposed by Buerger (12) emphasizes the importance of arteriosclerosis as the essential lesion in the production of gangrene complicating diabetes. This author's (12) excellent book contains a detailed description of the pathological findings.

**INCIDENCE:** Joslin (3) states that gangrene is responsible for 1/5 of all diabetic deaths in Boston. Morrison (13) lists gangrene as a contributing cause of death in 23% of the fatal cases of diabetes in Boston between 1895 and 1913. Other investigators (14) report gangrene as a complication in 7% of 963 patients suffering from diabetes, admitted to the Peter Bent Brigham hospital between 1913 and 1925.

In this latter series (14) all but 4 patients were over fifty years of age. In Joslin's (3) series, when the onset of diabetes was between the ages of fifty-one and seventy, gangrene developed in 3.6% of the patients. In those who developed diabetes after the age of seventy, 1 in every 5 had gangrene. This same series records no complication of gangrene in patients under the age of thirty-one.

Joslin (3) states that 55 of his cases occurred in males and 26 in females. In Blotner and Fitz' (14) series there were 33 males and 22 females.

Diabetic gangrene usually originates in the lower extremities. In the last named series (14), the lower extremity was affected 65 times and the upper extremity 4 times. In Eliason and Wright's (15) series the great toe was affected in 28 out of 55 patients. Next in order were the fifth, fourth, third and second toes. This held true also

for arteriosclerotic gangrene without diabetes. Comparing the site of the original gangrene with ultimate fatalities, the percentage of death was greatest when the third toe was the original site. Next in order were the second, fourth, fifth and first toes.

Gangrene of other portions of the body, though rare, is reported (16, 17, 18, 19, 20, 21), as is its occurrence in juveniles (22).

*SYMPTOMATOLOGY:* A detailed description of the symptomatology of the various types of gangrene complicating diabetes will not be attempted. In the type primarily caused by arteriosclerosis, the appearance of a black spot or dark bleb may be preceded by burning, tingling or pain in the affected extremity and by intermittent lameness. There may be a history of trauma, such as stubbing the toe or stepping on a rock. In the infected type, the blackened infected area may follow the paring of a corn, a pin scratch, injury from a nail in the shoe or other trauma.

In the neuritic type, a painless perforating ulcer develops insidiously on the heel, the great toe, or under the distal end of the metatarsal. When seen early, arterial pulsations may be felt in the foot, but the Achilles and patellar reflexes usually are diminished or absent.

*MEDICAL VERSUS SURGICAL TREATMENT:* An analysis of the literature shows that when intensive conservative measures are employed as outlined by Stetten (23), McArthur (24) and Bernheim (25), results are very favorable.

Blotner and Fitz (14) state that ex-

cept in some patients with superficial gangrene, there have been few cases which have healed spontaneously under medical care. Their medical efforts were confined to keeping blood sugar concentration and urine normal and treating the gangrenous part by heat, massage and other forms of physiotherapy.

Joslin (3) urges surgery at an early stage. He states that he has seen the bad rather than the favorable cases and this experience has probably led him to this decision.

Eliason and Wright (15) have recently analyzed 55 cases in which amputation was done for gangrene complicating diabetes and conclude that early high amputation is advisable in most cases.

*SELECTION OF CASES FOR MEDICAL TREATMENT:* Patients who show early signs of demarcation and sulcus formation separating the dead tissue from the living should be treated medically. Fulminating gangrene calls for immediate surgical attention. The decision as to the type of treatment in the borderline cases should only be made after careful consultation between surgeon and internist.

Each patient requires individual judgment. The following are the important points to be considered in deciding upon the safest and best method of procedure:

1. *History and Physical Findings:* The rapidity of the spread of the gangrene prior to hospitalization, the physical findings on entry, and the laboratory data regarding the diabetes or

other complicating conditions, are paramount factors in rendering a decision as to the type of treatment.

2. *Severity of the Diabetes:* If hyperglycemia is still present, with sugar in the urine, further dietary regime and insulin therapy may result in definite demarcation with regression of the gangrenous process. If the blood sugar is maintained at a fairly normal level with absence of sugar in the urine for many days and the gangrenous area progressively increases in size, surgery is indicated. If dietary regime, supplemented by insulin, fails to render the patient sugar free and the process is slightly but progressively advancing despite vigorous conservative means, the surgical consultant is justified in demanding that amputation be done without further delay.

3. *Degree of Vascular Occlusion:* The ultimate success or failure of treatment depends on the degree of patency of the vascular channels. Tests for circulatory sufficiency are of aid in determining the degree of obliteration of the vascular supply. Roentgenograms are very valuable in outlining arteriosclerosis. New methods of demonstrating the vascular tree to show the degree of thrombotic or athromatous occlusion are described by Brooks (26, 27) and others (28, 29, 30). With each of these procedures exposure and temporary ligation of the main arterial trunk is necessary before the radio opaque substance can be injected. The ischemia produced by even temporary ligation is dangerous in the presence of gangrene, especially in those cases in which conserva-

tive measures are contemplated. Ligation of the main arterial supply is considered dangerous by Buerger and others (31). However, ligation of the femoral artery has been recently advised as a therapeutic measure (32).

The French (33) use the oscillometer of Pachon in estimating the arterial circulation in the limbs and consider it the best available method for determining the degree and location of obliteration.

The intracutaneous salt test (34) is simple and safe and may be done on every patient. It is stated that the disappearance of the wheal in from 10 to 25 minutes is strongly suggestive of developing gangrene.

4. *Extent of the Gangrene:* It is difficult to formulate any set rules for guidance regarding the extent of the gangrene in selecting cases for treatment. There are many contingencies such as infection, extension of the process, location and degree of vascular occlusion modifying any general principles one may formulate. The prognosis in non-infected gangrene is of course better than in the infected type.

The following rules are applicable in determining conservative treatment in the infected type: (a) If the gangrenous process is limited to the digits, even though the phalanx shows necrosis, the chances for demarcation and spontaneous amputation with cure, are excellent. (b) If the gangrenous process involves the foot without death of more than 1/8 of the soft tissues and without signs of necrosis of bones other than the phalanges, the prognosis is fair. (c) If 1/8 to 1/4 of the dor-

sum or plantar surface of the foot is dead, or if the gangrene of the foot is complicated by necrosis of the bones of the foot other than the distal tip of the metatarsals and phalanges, conservative measures probably will not be successful. Roentgenograms are valuable in determining the amount of bone necrosis.

5. *Pain*: This is usually not so severe in the diabetic type of gangrene as it is in other types. Contrast baths may be of benefit; in fact some patients discover this method of relief before consulting a physician. Usually the pain is alleviated after the patient has had the advantage of the measures advised to enhance the circulation of the affected extremities.

6. *The Economic Aspect*: It is unfortunate that the economic situation should be an important factor in rendering a decision. However, if conservative treatment is not available at a low cost, amputation may be necessary for those patients who are unable to afford long hospitalization.

7. *Cooperation*: Before beginning treatment it should be explained to the patient that considerable time is required to secure results and that his strict cooperation will be necessary. If the individual's personality suggests that his cooperation will not be obtainable, he should be treated surgically.

#### CONSERVATIVE TREATMENT:

1. *Diet and Insulin* are directed along the same lines as for any diabetic patient over fifty years of age. The diabetes is usually of long standing and mild. However, the presence of

infection may seriously lower the carbohydrate tolerance. The caloric intake should be regulated to maintain optimum nutrition. The patient should not be allowed to become overweight. The findings of Letulle (7) and others lead us to conclude that perhaps a high fat diet contributes to the production of arteriosclerosis. Since we are interested in arteriosclerosis as well as diabetes as an etiological factor and problem in treatment of diabetic gangrene, a low fat diet may be advisable as a prophylactic measure.

2. *Rest in Bed*: Activity calls for increased blood supply which the atheromatous and occluded arteries are unable to furnish. At rest, nutritional demands are minimal and the supply may be sufficient to carry on until a more generous collateral circulation is established. Simple exercises should be carried out daily. The use of "blow-bottles" may be valuable in preventing respiratory complications.

3. *Position*: As pointed out by Buerger (12), the level at which the color of the affected part is nearest normal should serve as the patient's horizontal resting position. In the presence of gangrene this position of maximum circulatory activity is usually below the horizontal plane. The bed should be so arranged as to maintain this position at all times.

4. *Postural Treatment*: Buerger's (12) postural treatment is contraindicated in the presence of gangrene. It is not only difficult to carry out, but may cause severe pain. The ischemic phase of this therapeutic measure is dangerous when the blood supply to the extremities is minimal. With fre-

quent change in position, there is greater liability to injury, with serious consequences.

5. *Fluids*: In 1912, Mayesima (35) reported an increased blood viscosity in thrombo-angiitis obliterans with gangrene. He also noted that the blood viscosity could be decreased by infusions of normal salt solution with favorable effect on the gangrene. The following year, Koga (36) confirmed these findings and reported a series of 13 patients successfully treated by infusions of normal salt or Ringer's solution. In 1919, McArthur (24) used this same form of treatment in diabetic gangrene and reported favorable results in 9 patients. In addition to giving Ringer's solution by hypodermoclysis and intravenously, he introduced 3 to 4 litres of this solution into the duodenum by means of the Rehfuess tube. In most of the patients the extent of the gangrene was sufficient to have justified amputation. McArthur (24) stressed the importance of trying this conservative measure before resorting to surgery.

When treatment is first instituted, it is advisable to give as much fluid by hypodermoclysis as the patient is able to absorb, in addition to forcing fluids by mouth. At the end of a week, the patient can usually be persuaded to drink 6 to 10 litres of fluid in lieu of the hypodermoclysis. In some cases it may be advisable to give 200-300 cc daily of normal saline intravenously. In our experience, normal salt solution hypodermically and intravenously and water by mouth have been just as efficacious as Ringer's, Locke's, sodium citrate, or other solutions. The bene-

ficial effects probably depend upon the administration of fluid per se, rather than to the type of fluid administered. Owing to its greater penetration into the tissues, fluid by hypodermoclysis is possibly more valuable than an equal quantity taken by mouth. The daily intake should be at least 6 litres—the larger the amount, the more beneficial will be the effect.

There are no satisfactory scientific data to explain the beneficial effects of large quantities of fluid in the treatment of gangrene. Mayesima (35) advanced the theory that hypodermoclysis of normal salt solution favorably influences the progress of gangrene by decreasing the blood viscosity. Further studies are needed to confirm or disprove this theory. Stern lists one patient with diabetic gangrene and several other patients with various types of gangrene who showed normal blood viscosities.

6. *Thermotherapy*: The efficacy of superheated air has been pointed out by Méyer (37) and Stetten (23). Dieulefoy (38) has recommended its use at temperatures of 200 to 600 degrees, C., in exposures of one-half hour to three hours twice a day over the gangrenous area to prevent the spread of the process and hasten mummification. Stetten (23) has inserted the entire wrapped limb into a suitable oven and gradually worked up to temperatures of 180 to 200 degrees F. The maximum treatment advised was one-half hour twice a day if the patients were able to stand it. These treatments were followed by soaks in 100 degrees F. physiological salt solution for a half hour, immersing the entire limb.



This technique is difficult to carry out and exposure to high temperatures is dangerous, especially if the gangrenous area is infected. If the affected limb is kept constantly warm by a temperature of 100 to 125 degrees, F., better results are obtained. This may be accomplished by means of a carbon filament lamp, with reflector, attached to the roof of a cradle which has been covered with two or three thicknesses of blanket. A wire screen or guard over the light prevents any portion of the body from coming into direct contact with it. The apparatus is placed over the affected extremity and a switch placed conveniently at the head of the bed. The light is operated by the patient who soon becomes expert in maintaining the proper temperature. Treatment should be continuous during the waking hours. A constant vasodilation by reflex action is thus maintained. There have been no untoward effects or accentuation of symptoms from this treatment.

Hot compresses of 1-1000 neutral acriflavin or gentian violet are applied continuously to the affected part as long as infection is present. Heat is maintained in the compresses by the hot air apparatus. When the odor is particularly offensive, hot compresses of ¼% phenol solution are used. This causes very little, if any, devitalizing effect on the tissues. When infection is no longer present, compresses may be discontinued. In this stage exposure to sunlight or the Quartz Mercury Lamp may aid granulation.

7. *Diathermy*: Theoretically, diathermy should be of infinite value as it warms the deeper tissues and pro-

duces vaso-dilation of the smaller arterioles and capillaries. In 1915, Wolf (39) treated a diabetic woman seventy-eight years old, who suffered excruciating pain from an arteriosclerotic gangrenous ulcer on the plantar side of the little toe. By the use of diathermy, the ulcer healed in four weeks and did not reappear. Cluzet and Chevalier (40) report five cases of moist gangrene of the leg and one case of moist gangrene of the scrotum, completely cured by this form of treatment. Improvement was noted from the first treatment and the favorable effect on the circulation was shown by the change in the oscillometer record. Insulin seemed unnecessary for recovery. These authors believe diathermy may save similarly affected limbs from amputation. Lian and Descoust (41) are also enthusiastic supporters of diathermy and believe that it produces a local and general warming effect and intense vaso-dilation which assists the flow of blood into the smaller arterioles. In addition, they say that diathermy combats the spasms which are often concomitant and exercises an eutrophic action on the tissues, increasing their metabolism and improving nutrition. The results of other investigators have not been so encouraging. Buerger (12) says that diathermy is not well borne nor beneficial in the presence of inflammation, ulceration or gangrene.

Heat, however, applied, is of extreme importance in helping to re-establish circulation.

8. *Massage*: This form of therapy is considered inadvisable by some authors on account of the possibility of detaching thrombotic occlusions in

the vessels. The advantages of light effleurage are greater than the danger of embolism. It serves to maintain the normal tissue turgor and elimination from the skin. From the work of Boas (42), one may assume that reflex stimulation by massage may either cause relaxation of contracted capillaries or may increase the tone of the toxically paralysed smaller vessels whose lumens are obliterated by collapse of their walls.

9. *Medication*: The French (43, 44, 45) believe that sodium citrate by mouth is of definite value in the treatment of the various forms of gangrene. Labbe (4) states that the use of 20 to 30 grams daily may give good results by calming the pain and aiding the circulation. Our experience confirms these findings. Perhaps the beneficial effects may be explained by stimulation of the muscular tonicity of the vessels innervated by the sympathetic system.

Renaud (46) reports a gradual increase of both systolic and diastolic arterial tension following the injection of 8 to 12 grams of sodium citrate over a period of time. Four of our patients were given 12 to 16 grams of sodium citrate by mouth for a period of eight months without any increase in systolic or diastolic arterial tension, in fact both determinations were lower than before the administration of sodium citrate.

Mayesima (35) believed that the internal use of potassium iodide by those suffering from gangrene exerted a beneficial effect by decreasing the blood viscosity. These observations have not been confirmed. It may be

of value in promoting the absorption of cellular exudates and should be included in the patient's medication. It is prescribed in 2 cc. doses of the saturated solution three times a day.

If pain is severe, pyramidon, atropin or a combination of acetyl-salicylic acid and morphine may be tried for relief. Vasodilators are usually of no benefit.

If syphilis is suspected despite negative tests, approved anti-syphilitic treatment should be given. In these cases mercury ointment may be massaged into the skin overlying the main vessels of the extremities. Anti-syphilitic treatment is particularly efficacious in the neuritic type of gangrene.

Thyroid extract to the point of toxicity may be prescribed, especially if the basal metabolic rate is low. Physiologically it is said to produce dilatation of the peripheral vessels.

The possibility of tetanus (47) and gas gangrene must also be kept in mind. It may be advisable to give periodic prophylactic doses of tetanus antitoxin.

10. *Vaccine and Protein Shock*: Singer (48) has used intramuscular injections of caseosan with very favorable results in three cases of extensive diabetic gangrene. Pchellas (49) reports success in one case, by the use of mixed infection phylacogen.

11. *Drainage*: Infected moist gangrene is the type usually seen complicating diabetes. Proper drainage should be instituted early and the patient's progress followed by the surgeon. The area should be inspected and probed daily to open up any suspicious areas in the wound.

12. *Occupational Therapy*: Even with a satisfactory condition of the affected extremity a problem still remains in the preservation of the patient's morale. Basket weaving, tapestry or rug making and other forms of handicraft may be taught and some patients become very adept and enthusiastic workers. Sale of these products may help solve the financial problem.

#### *COURSE IN THE HOSPITAL:*

If progress is favorable, the sulcus of demarcation gradually becomes wider, exposing the pale red cross section of skin on the healthy side. The black skin covering the affected portion becomes progressively dryer and contracts, exposing the white, necrotic grayish-pus soaked deeper tissues. The under surface of the skin covering the viable area presents the same appearance. The phalanx, if exposed, is soft and spongy. Sooner or later, spontaneous amputation occurs. Visualize strands of fascia and tendons with mushy shreds of muscle and protruding necrotic bone with a grayish-black offensive purulent discharge and you have a fairly accurate mental picture of the progress so far.

The discharge becomes progressively less and the wound looks cleaner. Long strands of dead tendon and fascia may now be snipped off, but no attempt should be made to pull these strands out from the wound or pull on them so that they may be cut off as short as possible as this may result in reinfection and loss of tissue above the line of demarcation.

The picture now is much more encouraging and the patient is happy be-

cause he can see favorable progress. As the wound is probed for small collections of pus, blood oozes freely from the solid, red, healthy granulations. The threads of diseased tissue and the remaining parts of the bone slough off and healthy tissue fills up the site. Epidermatization is followed by discharge from daily observation.

The usual duration of treatment is from two to six months, depending on the severity and extent of the gangrene and the degree of vascular occlusion.

#### *DISCHARGE INSTRUCTIONS:*

At the time of discharge from the hospital, a written detailed list of instructions should be given to the patient. This is of supreme importance. Joslin (3) stresses the necessity of "keeping the feet as clean as the face." The patient should be warned against all factors such as prolonged standing, long walks, tight shoes, elastic bands, etc., which tend to disturb the fine balance between arterial sufficiency with tissue preservation and arterial insufficiency with trophic changes. Any tissue damage, such as abrasions, scratches, blisters or burns, however trivial, should be given immediate and careful attention. Before cutting nails the feet should be thoroughly cleansed and bathed in alcohol and all soft tissue injury should be avoided. Long nails, or sharp points left after cutting may produce injury leading to serious consequences. Corns, bunions and ingrown nails should be treated by a surgeon. In the event of any infection the patient should report immediately. Hose of suitable thickness should be worn so that the feet are kept comfortably warm. When the

patient is at leisure, the shoes should be removed and the feet elevated to the angle of circulatory sufficiency.

Tobacco and alcohol are prohibited. The daily fluid intake should be from 3,000 to 4,000 cc. The blood sugar concentration and urine should be kept normal by suitable diet and the use of insulin. The patient's weight should not exceed normal. An apparatus such as described for maintaining hyperemia can easily be made by the patient for use in his home. After discharge from the hospital, the extremities should be placed in this hot air apparatus for at least three hours daily. In some cases a longer exposure may be advisable.

Instruction regarding Buerger's (12) postural treatment should be given and one to three seances daily of this form of therapy may be very valuable as a prophylactic measure. Sodium citrate in 2 dram doses three times a day should be continued as well as the potassium iodide. The patient is, of course, instructed to report immediately if sugar occurs in the urine. Periodic fasting blood sugar determinations are made once a month or oftener.

The value of prophylactic treatment should be reiterated each time the patient is seen. The gospel of prevention should be impressed upon every diabetic, particularly those over fifty years of age. If he is inclined to belittle the possibility of gangrene as applied to himself, he may be impressed by a visit to the hospital to see the effects, on other patients, of neglect of prophylactic measures.

The liability to recurrence is the greatest hazard following discharge

from immediate supervision. If the patient conforms strictly to the instructions given on discharge, the probability of recurrence is minimized. If a comprehensive course of treatment directed toward maintaining circulatory sufficiency has been given, a recurrence of gangrene following trauma or infection usually clears up after a short stay in the hospital on the regime advised. This is exemplified by the following case reports:

Mrs. A. H., age 69, July 6, 1925. Duration of diabetes 12 or 13 years. Local trouble began one week before entry, following stepping on a rock. Chronic ulcer at the plantar base of the second left toe, for 4 months.

Examination: Phlegmon at the anterior base of the second left toe, ulcer about the size of a dime at the plantar base of the second left toe, with discharging sinus, area of infected moist gangrene about the size of a dollar on the mid-plantar surface of the left foot; foot red and edematous. Fever 100. Marked arteriosclerosis. No pulsations felt in the foot. Popliteal pulse feeble. General condition fair. Blood sugar 285.7 mgm. per 100 cc. of blood. Blood Wassermann negative. Urinalysis: sugar 3.8%, diabetic marked, acetone moderate; albumin trace; occasional hyaline and granular casts.

Routine conservative treatment, with incision and through and through drainage of the ulcerated and gangrenous areas.

November 2, 1925: Foot almost healed. The patient's condition satisfactory for discharge, but she preferred to remain until the foot was entirely healed.

December 24, 1925: Patient discharged. Foot completely healed.

March 9, 1926: Patient re-entered the hospital: Had stubbed left foot three days before entry.

Examination: Gangrenous blebs on the tip of the great toe, the tip and side of the little toe and several blebs along the lateral side of the left foot. Blood sugar 190 mgm.

per 100 cc. of blood. Urinalysis: sugar negative, diacetic and acetone negative.

April 15, 1926: Patient discharged. Foot healed. No recurrence to date.

Mrs. E. B., age 69, May 2, 1926. Duration of the diabetes unknown, estimated about 7 years. Three months before entry, infection of the right great toe followed the application of a corn plaster. The area had been discharging for two weeks.

Examination: Moist infected gangrene of entire right great toe. Foot swollen and edematous. Blood sugar 377 mgm. per 100 cc. of blood. Blood Wassermann negative. Blood plasma CO-2, 38.5 cc. bound as bicarbonate by 100 cc. plasma. Urinalysis: sugar 4.8%, acetone and diacetic negative, albumin trace. Routine conservative treatment instituted.

June 12, 1926: Toe sloughed off.

July 18, 1926: Patient discharged; foot healed except for a very small denuded area. September 29, 1926: Re-entered hospital. On September 16, ran a small nail into the mid medial surface of arch of right foot with subsequent infection of this area and the side of the foot. Sugar found in the urine for 4 days before entry.

Examination: Gangrenous phlegmon of the arch of the right foot. No sugar in the urine.

Incision of the area with drainage.

October 13, 1926: Patient discharged with a slight drainage from the site of incision but in a satisfactory condition. No recurrence to date.

In the past, attention has been directed principally to the dietary treatment of diabetes and the surgical treatment of gangrene. However, there have been reports (50) of successful conservative treatment of diabetic gangrene antedating the advent of our modern treatment of diabetes. Since the discovery of insulin and the newer methods of dietary administration, the treatment of diabetes has been revolutionized.

DuPre (51) and others (52, 53) have reported remarkable results in the conservative management of gangrene by the use of diet and insulin alone.

Insulin is an invaluable aid in quickly controlling diabetes even in cases of infected moist gangrene, thereby improving the patient's nutrition and increasing his resistance. By this indirect effect it is of inestimable value in the treatment of diabetic gangrene. This is shown by the figures of Blotner and Fitz (14):

Of 13 cases treated medically  
without insulin ..... 3 died

Of 11 cases treated medically  
with insulin ..... 2 died

Of 40 cases treated surgically  
without insulin ..... 10 died

Of 9 cases treated surgically  
with insulin ..... 1 died

Of 53 cases, medical and surgical, treated without insulin, 13, 30% died

Of 20 cases, medical and surgical, treated with insulin, 3, 15% died

Infection, although still a very potent factor, is not so serious in dealing with diabetes as it was before the use of insulin. With the application of ordinary surgical principles, ulcers, abscesses and other infections, including osteomyelitis, rapidly clear up, after the urine has become sugar free by the aid of insulin.

Time and expense are the principal objections to medical treatment. Unless these objections are insuperable, the patient is more than compensated for the expenditures by the preservation of his extremities.

Results from surgical treatment of diabetic gangrene are not particularly encouraging. Joslin (3) says that of 43 of his patients treated surgically, 15 or 35% died during the first year. Eliason and Wright (15) give their mortality as 43.6% in a series of 55 cases.

When amputation is necessary, it should not be the sole method of treatment. Following operation all patients should receive the benefits of the treatment outlined for increasing the circulation of the extremities. The advantages are noticeable in the rapidity of healing of the stump. Most surgeons do not consider this phase of the treatment of diabetic gangrene, and fail to give the patient adequate instructions relative to prophylaxis on their discharge from the hospital.

In advanced cases in which amputation is definitely indicated, but refused, remarkable results may be obtained and the patient's life saved by adequate conservative treatment.

If patients suffering from diabetic gangrene are given the advantage of the measures outlined for enhancing the circulation in addition to approved treatment for their diabetes, many favorable reports from conservative treatment will be recorded in the literature in the future.

Try conservative treatment in selected cases of diabetic gangrene, but do not let your enthusiasm replace sound judgment. Be conservative as long as progress is satisfactory, but be open to conviction if surgical counsel doubts favorable progress and suggests possible beginning toxemia.

#### CONCLUSIONS

1. Selected cases of diabetic gangrene including the moist infected type may be successfully treated by conservative measures.
2. Gangrene of sufficient extent to ordinarily justify amputation of the extremity may be treated conservatively and the extremity saved. Many of these gangrenous extremities which might have been saved by conservative measures have been sacrificed.
3. Too little attention has been paid to conservative measures which enhance the circulation of the gangrenous extremity. When treated surgically, the patient should have the advantage of these measures before and after amputation.
4. Insulin is of inestimable value in the treatment of diabetic gangrene in that it quickly controls the diabetes, thereby improving the patient's nutrition and increasing his resistance to infection.
5. Prophylactic treatment should include all measures which improve the circulation of the extremities.
6. If treatment is continuously employed to improve the circulation of the extremities the possibility of recurrence of gangrene is minimized.
7. If the patient has had a comprehensive course of treatment directed toward maintaining circulatory sufficiency, recurrence of gangrene following trauma or infection usually clears up after a short stay in the hospital.

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# The Relation of Trauma to Cardiac Disease

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THE medico-legal phase of the problem whether indirect injury to the thorax can induce temporary or permanent damage to the myocardium is sufficiently important to justify the addition of one other case report of this type. The medical expert is frequently in grave doubt whether a myocardial involvement or a disturbance of rhythm should be ascribed to a previous injury or trauma. Included in this category is the matter of heat exhaustion or heat stroke as a factor in the production of permanent myocardial involvement with a disturbance of rhythm. The matter is of considerable interest to clinicians aside from its very practical importance in a legal way.

Bockbank, in his book on "Incapacity and Disablement in its Medical Aspects," states that he has not seen evidence that auricular fibrillation could be brought on by sudden strain and that he is unwilling to believe that such strain could produce it. He does not make clear in this opinion whether he refers to strain superimposed upon damaged hearts, or whether he has reference only to hearts not previously involved.

The opinion that auricular fibrillation occurs only in hearts which have been damaged by existing pathological changes of whatever nature, undoubt-

edly holds true in the great majority of cases. The fact that such pathological change had not previously been demonstrated does not invalidate this opinion. The medico-legal bearing of this problem has to do also with the production of cardiac arrhythmias and their resultant conditions in hearts which have actually shown pre-existing damage. The law does not hold that an employer is free from responsibility, even though the heart were not entirely normal prior to the injury or strain. The role of the injury in bringing about the cardiac condition as determined at the existing period is a question to be determined at the legal investigation.

The second problem to be considered in this consideration is the possible effect of a temporary auricular fibrillation in its tendency to recur or become permanent. The fact that auricular fibrillation tends to recur in cardiac states even after long periods of absence is well known. Whether a heart which has undergone fibrillation following injury will have this same tendency to recur or become permanent is an unsettled problem. The presence of auricular fibrillation is undoubted reason for damage claims for disability. Also, the future probability of an individual to have a recurrence is a very practical consideration in the

assessment of damages or the placing of responsibility.

It is hardly necessary at this point to list the symptoms of auricular fibrillation as impediments to an employee. The increased shortness of breath, the cardiac or thoracic distress, the mental and nervous symptoms, are all well known and grave hindrances to normal productivity on the part of individuals engaged in any occupation.

Eyster and Swarthout estimate that auricular fibrillation in dogs decreases the output of the heart by 40 per cent, even when the myocardium is normal and the irregularity has been brought on by experimental means. This very considerable decrease in the cardiac output indicates how poor and inadequate is the circulation in this form of arrhythmia. This decrease in flow from the heart necessitates the great increase in the rate which often reaches figures of 140, 150, or 160.

Every physician has had the experience of meeting in his practice individuals showing auricular fibrillation who have not been aware of such disability. Such individuals may not have complained of cardiac symptoms, but a careful analysis of their history reveals a definite slowing down of their activities and a disinclination to prolonged or arduous labor and strain. There is a second group in which the fibrillation follows definitely a particular cause, with or without immediate recognition of the time of its onset. Such predisposing causes are numerous, including thyroid states, infectious diseases, and other well known conditions.

Hay and Jones (1), who have recently written upon this subject, listed

instances of auricular fibrillation following, respectively, exposure to electric current, sudden physical effort and alarm, following a struggle, and onset after sudden effort and lifting heavy weights.

Gossage and Hicks (2) reported several cases in 1913 in which the fibrillation occurred without apparent reason in young patients with apparently healthy hearts. This possibility does not seem so likely to occur at the present time with our greater opportunities for recognizing obscure thyroid states and other infectious processes.

The instance I wish to record is as follows:

A. G. Age 20. Occupation, truck driver. This man was admitted to St. Vincent's Hospital April 24, 1927, with the history that while engaged in some repair work on his truck train, he was caught between two trucks and rather severely crushed in the thoracic region. He was not rendered unconscious and there were no fractures determined by the x-ray. There were no external wounds, cuts, or lacerations, when he was seen shortly after his injury. Later, a few discolorations appeared from bruising. However, there was no question that he sustained a very severe crushing injury by two trucks which were forced together with him between.

The patient complained of severe pain in the thoracic region generally and also of marked distress in the cardiac region and breathlessness. He was not cyanotic. Examination showed very definite auricular fibrillation. The heart action showed complete irregularity when he was first

seen by me. The heart rate was counted at 150. The pulse was 60, but this could not be determined with absolute accuracy. There was considerable tenderness over the chest region generally. The pupils of both eyes

was not secured during these first few hours, but he was too sick to be moved. Any movement caused him much pain and greatly increased his breathlessness. However, it seemed to me that there was no question whatever that

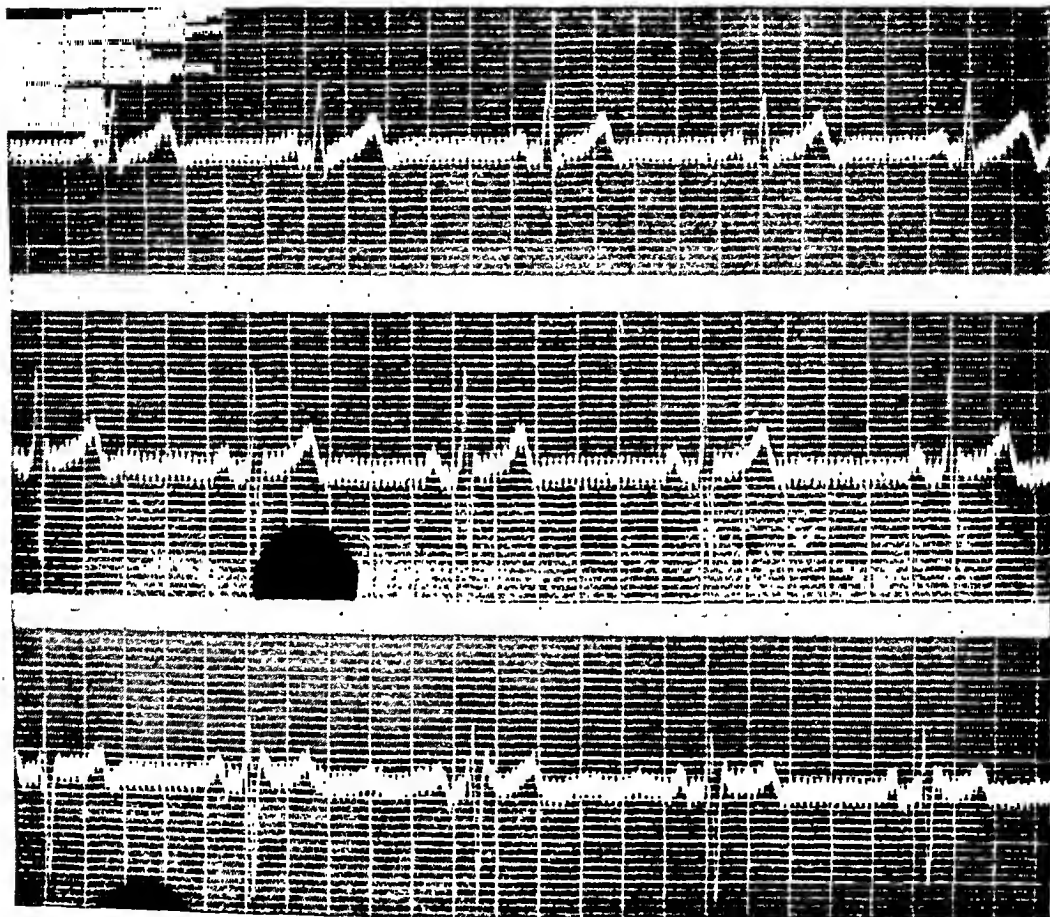


FIG. 1. Electrocardiogram 36 hours after injury.

were considerably dilated. The patient was weak, but clearly conscious and able to speak without any trouble. Deep breathing was difficult on account of the painful movement of the respiratory muscles. This patient was seen also by Dr. Thomas Crinnion and Dr. Frank Clifford. The auricular fibrillation persisted for 24 hours. It is regrettable that an electrocardiogram

there was an absolute irregularity of the heart action, that is, an auricular fibrillation. The increased rate and the great pulse deficit further supported this diagnosis.

#### FIG. I

An electrocardiogram was taken 36 hours after the injury. (Fig. 1.) This examination showed the P-R interval

0.18, the Q-R-S complex 0.08 in duration. The T waves in leads I, II, and III were abnormally large. There was definite left ventricular preponderance. The rhythm showed very moderate sinus arrhythmia. The heart action seemed to be normal in a clinical way at the time this electrocardiogram was obtained. The patient complained of considerable pain in the region of his thorax and back, but the sense of cardiac distress and breathlessness was absent. The increased heart rate had returned to normal and the pulse deficit was no longer present. Blood pressure was 120/82.

Later, when this patient had apparently recovered, he was subjected to a very careful examination and analysis of his previous life, working conditions, and possible symptoms. It was

brought out very definitely that he had always been well and as far as he knew had never had any symptoms which could possibly be connected with his heart or which impaired his working capacity. Clinical examination of the heart later has not revealed any evidence of cardiac disease in any way. The heart and blood pressure are apparently entirely normal. Physical examination generally did not reveal any thyroid disease, toxic state, or infection, which might have brought on a transient period of fibrillation. It is my impression that the fibrillation in this case was brought on by the crushing injury to his thorax. The question whether there will ever be a tendency to a recurrence of this form of cardiac arrhythmia in his case can not be answered at this time.

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# Basal Blood Pressure in the Normal\*

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**P**ROBABLY one of the greatest advances in internal medicine during the last half century has been the increasingly more common recognition of the fact that the important consideration in evaluating the condition of the heart is its capacity for doing work. Today the detection of murmurs is only a small part—and often an insignificant part—of the problem of estimating the health of the heart.

Similarly the mere determination of a blood pressure of a given number of millimeters falls far short of giving us a definite prognosis of any case. Ehrstrom (1) in analyzing a group of 20 who were observed ten to sixteen years with a blood pressure constantly (or nearly so) of two hundred or more found that they felt and looked well and continued to work. From a study of 300 cases he comes to the conclusion that the chances are about even as to whether a high blood pressure means a shortening of life. Even in hypertensive patients with heart disease he found unexpected remissions or long tolerance.

Because of this wide variation in significance of any blood pressure find-

ing even with the utmost care in the selection and manipulation of the instrument and the proper control of the individual, numerous attempts have been made to develop tests which would extend the value of blood pressure determinations.

One of the first questions to be answered by the physician who finds a pressure of say two hundred is whether or not that pressure is temporary and will soon pass away or whether it tends to remain at that level and will not only not drop spontaneously but will be resistant to treatment. Of course a due consideration of all the data from a complete physical examination is necessary in the interpretation of any blood pressure finding, but this study at the best gives only indefinite information.

One of the most recent attempts to find a more definite answer to the question of the significance of a high blood pressure determination is reported by Sladen and Johnston (2). The blood pressure is taken under conditions somewhat similar to those required for the determination of the basal metabolic rate. This is called the basal blood pressure and very often it is found to be much lower than a reading obtained on first examination. Immediately afterwards a simple exercise is given and the systolic blood

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pressure taken at one-half minute intervals following the exercise and a graph plotted of all the determinations. According to these workers, if the curve rises immediately after the exercise and then falls sharply, reaching a level considerably below that basal rate in a few minutes, the prognosis is most favorable. On the other hand if there is only a slight and gradual fall and the basal rate is not reached, then there is little hope of effecting any considerable decrease in the blood pressure of that individual by any method of treatment and the patient must adjust his life permanently in accordance with the limitations set by that pressure.

Unfortunately only three cases are reported on which this test was made. Because of the simplicity of the test and because of the importance of the problem involved, it was thought advisable to investigate the test further and to begin doing this on the apparently normal individual. It should be pointed out that the following data are not presented as being contributions to the large problem of the effect of exercise on blood pressure, especially since it is realized as pointed out by MacWilliam (3) that it is necessary to measure the pressure during exercise if the complete picture of the changes is to be obtained. Rather was this study instituted as a beginning to ascertain whether the apparently normal individual reacted with any degree of constancy to this particular test.

The subjects chosen were university students of both sexes who volunteered for the test. They were in all cases in excellent health and were in rather better than average physical con-

dition, being for the most part majors in the school of physical education. Not only were they quite used to having blood pressure taken but they also had this test described to them in detail. At the time an appointment was made they were given a mimeographed statement of what was expected of them with an explanation of just what was involved in the test so that they not only knew what to do but were free from any anxiety. To get their pressure at more nearly basal conditions they were asked to sleep in the University Infirmary and the test was made early the next morning before breakfast.

There were 28 men and 32 women tested. All of these had previously been found free of major defects and had had at least one normal urinalysis. A mercury manometer was used and all readings were taken with the patient recumbent—the cuff on the left arm. The exercise consisted in running up and down a flight of seventeen steps. For the sake of uniformity the men were all examined by the same physician as were the women. About half had their pulse rate recorded by an attendant, and in every case the pulse rate returned to approximately the rate before exercise in at least three minutes, and usually had returned to its original rate in one minute. The pressure was taken as soon after exercise as possible and thereafter at minute or half-minute intervals for about ten minutes. Both the systolic and diastolic pressure were recorded and the pulse pressure computed. Inasmuch as this work was undertaken as a study of the test advocated by Sladen and Johnston (1) in

which only systolic pressure is considered, it is only of our systolic pressure determinations that a detailed analysis is given in this report.

The most common type of reaction was an initial high rise followed by a sharp drop and then a very gradual drop to below the basal rate. This is the type of curve that Sladen and Johnston (1) consider of good prognosis. However, while this reaction is the most common, there is a high percentage of variations from it in the apparently normal. Tables 1 and 2 show

the time this fall continued varied from one to fourteen minutes. In 40% of those examined the systolic pressure did not fall below the original or basal rate. Probably if a more involved type of exercise had been used so that measurements could have been taken during exercise a more uniform type of curve would have been obtained.

An analysis of the diastolic pressures gave no more uniform results, for in 43% there was no change (or less than 4 mm. change) after this exercise test described above—in 17%

TABLE 1. Primary Change.

Changes from basal blood pressure (systolic) rate immediately after a given exercise.

Amount of change	Number of Men	Number of Women	Total	Percentage
Decrease of 4 mm. or more.....	2	2	4	6.7
No change .....	0	1	1	1.7
Increase of 1 - 3 mm. ....	3	0	3	5.0
" " 4 - 6 mm. ....	2	1	3	5.0
" " 7 - 12 mm. ....	6	7	13	21.7
" " 13 - 20 mm. ....	9	7	16	26.7
" " 21 mm. plus .....	6	14	20	33.3

TABLE 2. Secondary Change.

Change in pressure during rest period after exercise.

	Number of Men	Number of Women	Total	Percentage
No. dropped at least 4 mm. below basal rate	23	13	36	60
No. dropped to basal rate (or within 4 mm.)	4	13	17	28.3
No. that did not drop to within 4 mm. of basal rate .....	1	6	7	11.7

in detail some of these variations. From Table 1 it will be seen that about 18% of those examined gave a systolic reading immediately after exercise that was not appreciably higher than the basal rate and in about 7% was actually less. In all cases there was a fall from this reading taken immediately after exercise, but

there was a rise and in 40% there was a fall. The most constant finding was a rise in pulse pressure immediately after exercise which occurred in 52 or 87%. No appreciable change (4 mm. plus) occurred in 13%. There was never an initial fall in pulse pressure. This was the only constant finding.



*Conclusion.* The variations in the systolic (and diastolic) pressure response noted after a simple exercise test in 60 normal young adults were so great that it seems extremely doubtful whether the test can be of any clinical value at least in its present form. There was a marked variation in (1) the initial change, (2) the rate of fall and (3) the amount of the fall.

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# Torula Infection in Man

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ALTHOUGH medical literature records only a small number of cases due to infection with the yeast organism, *Torula histolytica*, it is assumed that many cases do occur but remain unrecognized. In 1926 Rappaport and Kaplan (1) reported the thirteenth case, the first one in which a lesion of the skin was described; Lynch and Rose (2) reported the seventeenth case, the infection involving the central nervous system; McGehee and Michelson (3) reported the isolation of the organism from a diseased gland in the groin of a negro, recovery following the excision of the gland; Prinz (4) reported a black yeast-like mold infection of the tongue; Alvarez (5) reported a red torula infection of the tongue. In 1927, Lloyd Jones (6) reported a torula infection involving the palate and nasopharynx, which apparently was arrested by careful cauterization and the therapeutic application of the x-ray, and the internal administration of potassium iodide. In the discussion of Jones' paper, Dr. Wm. D. Gill of Texas reported two cases, one of an ulcerative cutaneous lesion in the preauricular region on each side of the face which yielded to mild curettement, the x-ray locally and potassium iodide internally; the other infection involved the orbit and the sinuses of the head, and was accompanied by the presence of

the torula histolytica in the blood stream, the condition apparently becoming arrested by the daily administration of 120 grains potassium iodide internally, 15 grains of sodium iodide intravenously and x-ray exposures to the orbit and sinuses. Including the two cases of Gill, twenty-four cases have been reported in the medical literature.

The group of blastomycetes known as *Fungi imperfecti* is composed of *torula*, *oidium*, *monilia* and *dematium*. *Torula* is considered to be a pseudo-yeast, occurring abundantly in nature, on trees, fruits, bees, wasp-nests and insects, and has been found in canned butter and in milk. Yeasts are found in the throats of many individuals and under proper conditions they become pathogenic, setting up inflammation of the mucous membranes of the throat and air passages, also producing more deep-seated infections of the tonsil or peritonsillar tissue with a predilection for the central nervous system and lungs.

## REPORT OF A CASE

The condition was recognized by Dr. M. F. McCarthy of this city, who referred the patient to me for general treatment, after Dr. Geo. Rockwell had succeeded in isolating the organism from the lesion on the tongue following the methods employed by

Sheppe (7). Drs. McCarthy and Rockwell will make reports in special journals, listing special features and cultural characteristics of the organism isolated.

*History*—A man, aged 28, a laborer in a steel plant, suffered an injury to the anterior part of the tongue June 20, 1926, when a piece of hot steel flew into his mouth. He was given immediate attention by a physician, but this condition grew worse, the tongue gradually assuming the state as pictured in Fig. 1. He was an American by birth, of good family history, and had previously always been in good health except for an attack of acute appendicitis for which he was operated upon ten years ago, and for an attack of double pneumonia twelve years ago from which he completely recovered. He was married and had a healthy child. He had been examined for life insurance and accepted in April, 1926. The heart and lungs were found to be normal. Previous to the onset of the present illness, he weighed 206 pounds.

*Examination*—When I first saw him on January 11, 1927, he was considerably emaciated, weighing 146 pounds, felt weak and complained of pain in the tongue which caused inability to eat and sleep properly. He could speak with difficulty owing to the contraction of the anterior part of the tongue. His temperature was 100, and the pulse rapid. His appetite was good and he could only partake of liquid food. He was constipated as a rule. He complained of no headache or pains about the body except for a pain in the chest which he ascribed to pleurisy a week ago. He had no

precordial distress; was dyspneic on exertion. There were no genito-urinary disturbances.

The pupils were equal and reacted normally. There were no symptoms to indicate involvement of the special cranial nerves. The lips were normal. The upper teeth were missing, those remaining in the lower jaw were in poor condition and there was evidence of pyorrhea. The anterior part of the tongue was smaller than normal and partly bound to the floor of the mouth. The anterior third of the tongue was distinctly ulcerated, would bleed easily and was the seat of numerous small whitish masses composed of mucoid-like material. The remainder of the tongue was coated white, with a small elevated patch on the right side, somewhat discolored. The tonsils were not enlarged or infected. There was no enlargement of the thyroid, submaxillary or cervical glands.

The chest was well developed, expansion being good. The left border of the heart was within the left mammary line, there was no dilatation of the aorta, no murmurs were heard, the action was rapid but regular. The examination of the lungs showed no alteration to percussion on either side; wheezing râles were heard throughout both lungs, both anteriorly and posteriorly, but no other râles were heard. Inspiration was somewhat roughened and expiration apparently somewhat prolonged throughout. Over the right base roughened grating sounds were heard, which were thought to be due to dry pleurisy. A fluoroscopic examination of the chest made at this time showed the heart to be normal in size and position; there was diffuse en-

largement of the glands at the hilum most marked on the left side; the parenchyma of the lung was mottled throughout; the costo-phrenic angles were clear; the diaphragmatic movements free and equal.

The examination of the abdomen showed no enlargement of the liver or spleen; at a later date the spleen was

laris, infected teeth, diffuse pulmonary infiltration due to tuberculosis or torula infection, dry pleurisy of the right lower lobe.

#### *Special Examinations*

Urinalysis: Amber colored, clear, acid, specific gravity 1.010, sugar negative, albumin negative, diacetic acid



FIG. 1.—Showing ulceration of the tongue from which the *Torula histolytica* was cultivated.

felt. There was no tenderness over the gall bladder or appendix areas; there was no palpable enlargement of the glands. The extremities were normal; reflexes active. The rectal examination showed no enlargement of the prostate or seminal vesicles; no hemorrhoids were found.

As a result of the examination the following diagnoses were made: ulceration of the tongue, pyorrhoea alveo-

negative, indican negative. Microscopic: no casts, no red cells, no pus cells.

Blood count: fresh specimen showed rouleaux formation, no change in the outline of the red cells. Hemoglobin 80 per cent. Red cells, 4,900,000. Color index 0.81. White cells 3,850. Differential: 54.5 per cent polynuclears, 30.5 per cent small and 5 per cent large lymphocytes, 1 per cent

mast, 3.5 per cent eosinophiles, and 5.5 per cent transitionals.

Blood culture: negative.

Blood Wassermann: negative reaction using cholesterinized and alcoholic

Intradermic tuberculin test: negative.

Dr. Rockwell had isolated the *torula histolytica* organism in October, 1926, using 0.3% malt extract, dextrose, and

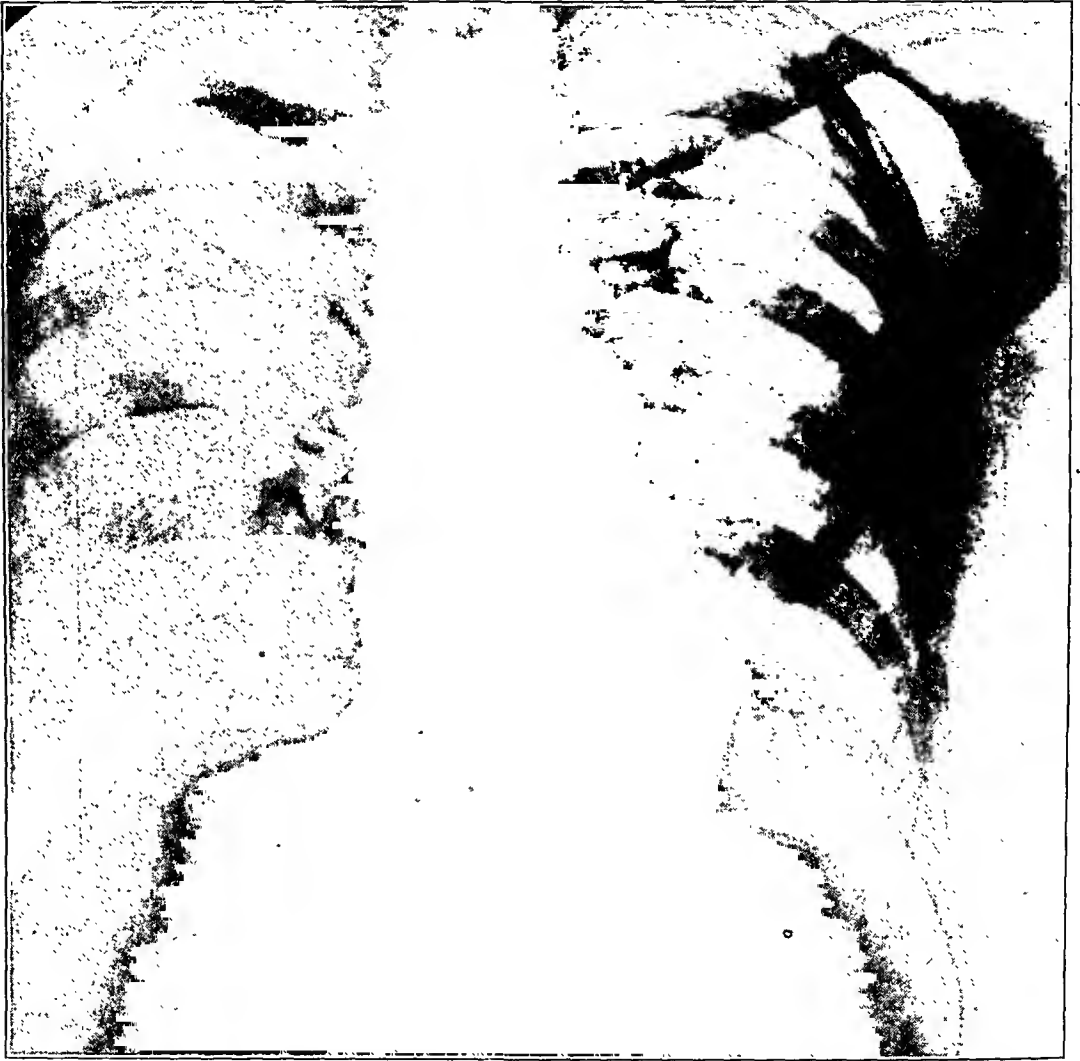


FIG. 2.—Stereoscopic picture showing diffuse bilateral infiltration, not typical of tuberculosis of the lung.

antigens with the method of ice box fixation.

Kahn precipitin test for lues: negative reaction.

Tubercumet test of the blood serum: positive.

maltose with lactic acid media; also staphylococci and streptococci with plain media. A small piece was excised from the margin of the ulcer and examined microscopically, but no evidence of malignancy was found.

X-ray examination of the chest by Dr. Chas. Goosmann in January, 1927: stereoscopic pictures showed diffuse bilateral infiltration, not the typical picture of tuberculosis of the lung.

X-ray examination of the teeth by Dr. J. P. Becker, April, 1927: x-ray does not reveal evidence of tissue change about the apex; however, the right and left molars are converged and rather deep pocket formation about these teeth. The lower anterior teeth appear to be quite normal. The position of these teeth may be causing some irritation to his tongue.

*Previous treatment and course:* Local antiseptic measures including the use of mercurochrome, acriflavine, gentian violet, dioxygen, perborate of soda and arsenobenzol in glycerine; one fifteen-minute exposure to the x-ray, followed by an exposure of one hour to radium, which caused considerable local reaction. In addition the patient was given a course of subcutaneous inoculations, using a vaccine composed of staphylococci and streptococci isolated by culture from the tongue, but with no favorable results. A boiled aqueous extract of the torula culture produced a very marked local skin reaction when given subcutaneously. The course was progressively downward.

*Subsequent treatment and course:* Following the suggestions of Alvarez (5), the patient was given two grain doses of quinine sulfate three times a day, and two intravenous injections of 0.6 gram neo-salvarsan. Apparently the patient was much benefited; he was in a different frame of mind and more hopeful; the pain in the tongue disappeared and he could sleep better and

eat solid food for the first time. The tongue began to improve; the temperature was 99.0. The pains in the chest disappeared, and the physical signs of the lungs had diminished, although the fluoroscopic examination showed the same infiltration. He now weighed 144 pounds. He was now given another intravenous injection of neo-salvarsan (0.6 gram) following which he grew worse. The use of quinine internally was continued and the internal administration of a saturated solution of sodium iodide, 15 drops three times a day, was begun. A week later general exposures with the ultra-violet mercury lamp were begun. The fourth and last intravenous injection of 0.6 gram neo-salvarsan was given four weeks after the third, followed by gastro-intestinal disturbances. A week later he again began to improve, both locally and generally. His weight remained about the same, 143 pounds, to April 5, 1927.

The period of improvement lasted about two weeks longer when there was a relapse, the condition of the tongue grew worse, the wheezing râles returned throughout the chest, the spleen grew larger and the temperature rose. An aqueous solution of acriflavine was used locally and 0.15 gram of the neutral acriflavine in 15 c.c. distilled water was given intravenously. There was no improvement. An injection of 0.3 gram neo-salvarsan was given intravenously on May 2, 1927. The patient grew steadily worse, the temperature rising to 101.4. He was now sent to a hospital and given a mild diathermy treatment locally to the tongue. The course was progressively downward, the patient

dying of inanition on May 17, 1927. We were very desirous of obtaining an autopsy, but this was denied. This was unfortunate in that a gross and microscopic examination of the lung and spleen in particular would have been instructive.

*Discussion:* A case of ulceration of the tongue is reported, in which the *Torula histolytica* was isolated from the lesion. The marked skin reaction following the subcutaneous injection of a boiled aqueous extract of a culture of the organism, indicates that a state of hypersensitiveness existed. Complications in the form of a mottled infiltration of the parenchyma of the lung and enlargement of the spleen, were present. The blood culture was negative. Unfortunately, permission was not granted to perform an autopsy to determine the character of the lesion

in the lungs and spleen. At no time was it possible to obtain a specimen of sputum to examine for tubercle bacilli. The patient had never worked in an atmosphere containing dust, so that the changes in the lung cannot be attributed to siderosis. Temporary improvement followed the employment of neo-salvarsan intravenously. Local antiseptic measures in the form of the various dyes, arseno-benzol, and perborate of soda were of no avail. The exposure to the x-ray and radium was followed by such a reaction that the patient did not care to have these repeated. No improvement followed their use. Quinine sulfate and sodium iodide internally over a prolonged period seemed to be of no benefit. Death was due to inanition, the patient steadily losing in weight and finally refusing food.

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# X-ray Treatment of Goiter

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THE indication for radiation treatment in goiter is hyperthyroidism, the contraindication is a normal or a minus metabolic rate. The exceptions to this rule are malignancy of the thyroid or inoperable intrathoracic thyroid. In the first instance, radiation may be used to supplement operative measures or as a primary treatment. In either case the prognosis is very grave. In intrathoracic goiter either with or without hyperthyroidism if operation is considered inadvisable, radiation should be instituted in an effort to reduce the size of the gland and relieve the pressure symptoms. In all other conditions of the thyroid gland radiation should not be used unless hyperthyroidism is present. If there is any doubt at all on this point the basal metabolism test should be the deciding factor. As a matter of fact, it is best to perform this test on all suspected thyroid cases. Personally, I do not treat thyroid cases unless they have a metabolic rate of plus 10 or more.

Hyperthyroids are commonly classified as (1) exophthalmic goiter and (2) toxic adenoma. For the purpose of discussing the treatment I will add to these (3) adolescent goiter and (4) hyperthyroidism without exophthalmos and with or without goiter. I am uncertain whether these two classes differ from exophthalmic goiter in any

respect except that of severity. Surely one occasionally sees exophthalmic goiter in an adolescent but the great majority of hyperthyroids at this age, if untreated, will gradually recover without going into an exophthalmic stage or else will develop adenomata. In the absence of exophthalmos I question the propriety of calling such cases exophthalmic goiter unless it can be shown that the natural progress of the disease will eventually develop an exophthalmos. In the majority of cases of hyperthyroidism around puberty this does not happen, but it is still possible that these cases differ from exophthalmic goiter in degree only and not in kind. The same remark will apply to the classification which I have designated as hyperthyroidism without exophthalmos and with or without goiter. I referred to these cases in an article published in 1922 (1) and since then have seen many more. The widespread use of the basal metabolism test has brought to light an increasing number of these cases, although I would hesitate to accept a plus metabolism as an evidence of hyperthyroidism unless such a diagnosis could be substantiated clinically. These cases all have the exophthalmic goiter syndrome but none have exophthalmos and quite a few are without much enlargement of the thyroid.

I believe the hyperthyroidism is



probably the reaction to some toxemia, not necessarily always the same. Many of these cases have definitely pathological tonsils, some have infected teeth. In a number it is not possible to discover any such source of infection or irritation, but there may be conditions present which we do not recognize as etiologic factors. For instance, McCarrison believes that intestinal intoxication may be a cause of goiter. Whatever the cause these cases are definitely hyperthyroid and they do not always recover from the hyperthyroidism when the exciting cause is removed, although it goes without saying that this is the first thing that should be done provided the cause is known. Radiation treatment is particularly successful in this class of cases and surgery correspondingly unnecessary. I have no data at this time to show whether these cases would eventually develop exophthalmos or not. It may be that this is simply an early stage of exophthalmic goiter now recognized at such a stage because of the universal use of the metabolism test. However, reference to the histories of the cases reported in this paper show that 32 cases of undoubted exophthalmic goiter gave a total duration of 289 months or an average of 9 months before I saw them. Twenty-eight cases classed as hyperthyroidism without exophthalmos gave a total duration of 294 months or an average of  $10\frac{1}{2}$  months before applying for treatment. Such a comparison, of course, proves nothing, but one cannot help but wonder why this group of cases had not developed exophthalmos in such a length of time if they were ever going to. That all exoph-

thalmic goiter cases are not due to one cause is proven by the fact that some come on suddenly after fright or shock and others develop gradually without any such etiologic factor. It is possible that the nature or severity of the etiologic factor may determine the development of exophthalmos, goiter, hyperthyroidism without goiter or adenomata. Perhaps the patient's inherent ability to combat the disease may bring about these variations.

It is generally accepted that the symptom-complex which is present in all the goiters which we are accustomed to speak of as hyperthyroids is due to an over secretion of the gland. However, this theory has been questioned lately by several authors, who suggest that the change in the secretion may be qualitative rather than quantitative. The Mayo Clinic advance the hypothesis that in toxic adenoma there is an increase in thyroid secretion in the blood, but that in exophthalmic goiter the character of the secretion is altered. Since the action of radiation on gland tissue is to produce an atrophy, if this theory is accepted, the rationale of radiation treatment might be seriously questioned. However, any one who cares to may watch a case of exophthalmic goiter being properly treated by X-ray and note the gradual subsidence of the so-called "hyperthyroid symptoms" and the corresponding fall in the metabolic rate. Whether this effect is due to an actual diminution in the quantity of thyroid secretion or to the destruction of gland cells which are throwing out a perverted secretion, the action on the patient is certainly beneficial.

The first step in the treatment of any disease is a correct diagnosis and too much emphasis cannot be laid upon the necessity of determining if a supposed thyroid case is suffering from hyperthyroidism. The symptom-complex is well known and consists of nervousness, tachycardia, goiter and exophthalmos. To these major symptoms may be added weakness, loss of weight in spite of good appetite, sleeplessness, digestive symptoms, profuse sweating and a sense of profound anxiety which is practically always present. These characteristic symptoms added to an increased metabolic rate make the diagnosis. I do not think a diagnosis of hyperthyroidism should be made on an increased metabolic rate alone, if these symptoms are absent, and would advise against X-ray treatment under such circumstances.

We will now consider the types of goiter enumerated in a little more detail.

Adolescent goiter—The physiological enlargement of the thyroid gland at puberty should never be mistaken for a pathological condition. It is practically always present in young girls at this age and calls for no treatment whatever. However, a small percentage of these children develop hyperthyroidism and occasionally true exophthalmic goiter. If the hyperthyroid condition is recognized and a small amount of X-ray treatment given the prompt recovery of the patient is extremely satisfying. I have had no experience in the administration of iodine to prevent the occurrence of goiter in adolescents, but I have seen quite a number of cases in

the last three or four years in which iodine was given to these little patients, who undoubtedly had nothing more than the normal physiological enlargement of that period, and a serious hyperthyroidism was brought on as a result of such treatment. As a matter of fact, this statement might be dilated on to include many cases of goiter in adults as well. There appears to be a widespread belief among the medical profession and the laity at large that iodine is a newly discovered and very effective drug in the treatment of goiter. Such is far from being the fact, as it is one of the oldest remedies used in this disease and its range of usefulness is quite limited.

The remarkable effects from the use of this drug at the Mayo Clinic to prevent post-operative complications in exophthalmic goiter has apparently led many members of the profession to believe that this is the drug of all others to use in the treatment of goiter, although Plummer who originated the treatment and many others who practice it enthusiastically are emphatic in saying that it is a method of preparing the patient for operation and not a method of treatment for the disease. In the last two years I have seen a great number of patients whose goiters were undoubtedly caused by iodine or made much worse by its administration. Some of these patients took iodine on their own initiative and others were given the drug by their physicians. Lahey, in discussing a paper by J. De J. Pemberton on this subject, expresses my own views exactly. He says: "It is the duty of all who deal with patients with disease of the thyroid firmly to impress on the

public that iodine is not a method of cure in exophthalmic goiter but a method of preparing patients for operation." While on the subject of iodine a word might be said about its use as a preliminary to X-ray treatment. There seems to be an impression that its effect would be the same for this purpose as it would if used as a preliminary to operation. I have used it in a few cases for this purpose but without effect on the course of the treatment so far as I could see. The pathological examination of thyroids removed after preliminary iodine treatment shows a marked increase in colloid material and a decrease in the size of the secreting cells. This would, in all probability, be an advantage to the surgeon but hardly to the radiologist as colloid is unaffected by radiation. However, the number of cases I have treated in this manner is not sufficient to justify any positive conclusions.

*Hyperthyroidism without exophthalmos and with or without goiter*—These cases have all the symptoms of exophthalmic goiter including a high metabolic rate but no exophthalmos and often very little or perhaps no goiter. Of the 36 cases reported in this paper 5 had no recognizable enlargement of the thyroid, 29 had a slight enlargement and 2 had well marked enlargement. They are commonly regarded as atypical cases of exophthalmic goiter, but I wish to question the propriety of such classification, especially as they are almost as numerous as the cases with exophthalmos. I feel certain that the thyroid gland is secondarily involved

from diseased tonsils in a fair proportion of these cases in much the same manner as the cervical lymphatics are. Such cases will often not improve from radiation of the thyroid alone but respond immediately if the tonsils are treated also. I suspect that abscessed teeth may be an etiologic factor and possibly focal infections in other parts of the body may also cause a reaction in the thyroid. A large percentage of these cases do well under X-ray treatment and surgery seems unnecessary except as a remedial agent for primary foci of infection. The enlargement of the gland in these cases is similar in character to exophthalmic goiter and is not adenomatous.

*Exophthalmic goiter*—There appear to be three definite varieties of this type of goiter. (1) Those having a sex basis and occurring near puberty, pregnancies or the menopause. (2) Those with neurotic basis and caused by fright, shock, worry and so forth. (3) Those in which the cause is undetermined. Although occurring from such different causes the disease is the same once it is established. It differs from the previous classification in that exophthalmos is a constant factor and the disease runs a typical course with remissions and exacerbations extending over a long period. It is differentiated from toxic adenoma by the character of the enlargement of the thyroid. In exophthalmic goiter there is a general enlargement either of one or both lobes, the gland is rather soft and may pulsate. In old cases, after repeated cycles of remission and exacerbation, adenomata are apt to be

present also. In adenoma there are one or more hard distinct nodules with well defined outlines.

In exophthalmic goiter, X-ray treatment is usually satisfactory, provided the case is seen before the first remission has occurred. After the case has gone through several remissions and exacerbations, the result is not apt to be so satisfactory. In 1917, I called attention to the fact that the longer a goiter had been present, the less likelihood there was of effecting a cure by radiation. My experience since that time confirms me in this opinion.

Severity of symptoms is not a contra-indication to radiation unless the patient is in a so-called "thyroid crisis," when she should, of course, be put to bed and given appropriate emergency treatment. Some of our most brilliant results have been in cases that had the most violent symptoms.

*Toxic Adenoma*—These cases are recognized by the presence of adenomata in the gland, combined with the symptoms of a thyrotoxicosis and an elevated basal metabolic rate. They are the least satisfactory of all hyperthyroids to treat by radiation in my experience. If operation is considered inadvisable, or refused, radiation should be tried, of course. However, I believe operation should have first choice, especially when one considers the possibility of malignant degeneration at a later date.

*Technic of Radiation*—This should be thought of primarily as a medical treatment and the same routine should be carried out as if the patient were going to be treated by medicine alone. That is to say, she should pay the

same attention to hygiene, rest, diet, etc. I tell these patients that there are four things that are absolutely essential to their recovery: 1. Rest. 2. Fresh air. 3. Good food. 4. Sleep. Above all, the patient must be relieved from worry and excitement. In the matter of food, red meat is not allowed; tea, coffee, alcohol and tobacco are also prohibited. Drugs are only given for special indications and not to combat the disease. It usually requires about six months to bring the case to a point where treatment can be stopped and the patient should be told this at the outset.

As regards dosage, I am in the habit of applying one-half an erythema dose of rays of a quality corresponding to a 9" parallel gap-filtered through 6 millimeters of aluminum, to one lobe of the thyroid each week. This gives a treatment over each area every two weeks. After two treatments are given to each area, the patient is given a rest from treatment for two weeks. This process is repeated as long as the treatment is continued. This is rather mild X-ray treatment and is not apt to produce skin changes or other untoward effects. Unless the patient comes from a distance and one wishes to save them the added exertion of frequent visits, it is wise to treat only one area each week rather than both areas every two or three weeks. By this method one has better supervision over the patient. This is quite important in patients as mentally upset as hyperthyroids whose daily habits and progress require the constant attention and supervision of the doctor.

Where radium is used, I apply half an erythema dose of gamma radiation

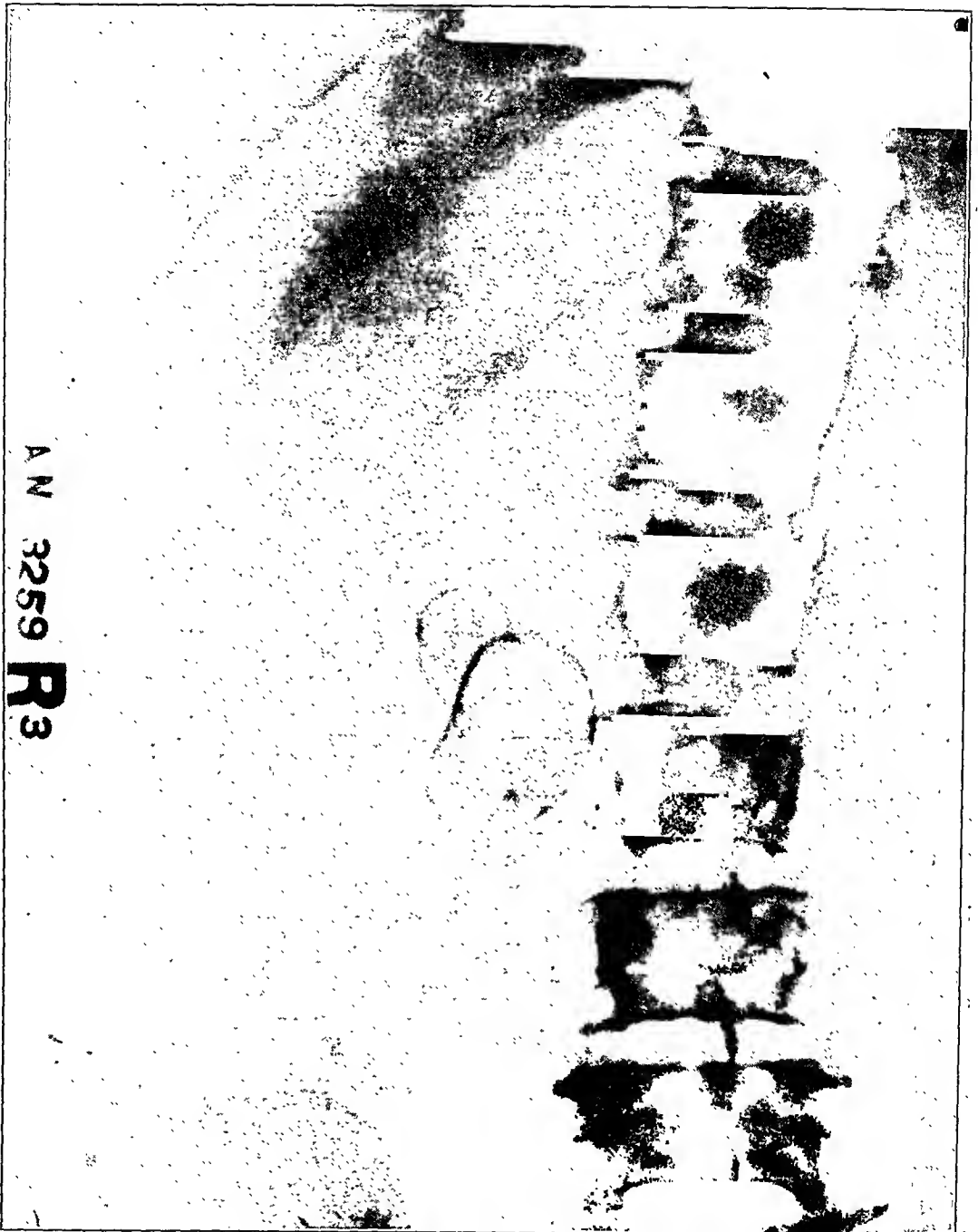


FIG. 1. Calcified Aneurysm of the Right Renal Artery.

Post-mortem examination (Dr. C. J. Bucher) showed an hypertrophied heart with myocardial fibrosis, large infarcts at the base of the right lung, a large "nutmeg" liver and a calcified aneurysm of the right renal artery, pressing upon the duodenum and pushing the kidney down. It was the latter organ that we felt as the firm tender mass below the liver. The right kidney contained a number of large anemic infarcts. The aorta was the seat of advanced atherosclerotic change but there was no evidence of syphilis.

#### COMMENT

Aneurysm of the renal artery is a rare form, constituting about 1.2% of all aneurysms. A total of 40 cases had been reported up to December, 1926 (1). The etiology is especially interesting. Among 31 cases collected by Conroy (2), 17 were traumatic and 15 non-traumatic. Of the latter 6 were associated with arteriosclerosis and 9 followed severe infections. In this connection attention may be called to the similarity of etiologic factors in aneurysms of arteries to other abdominal viscera. Among 65 cases of aneurysm of the hepatic artery collected by Friedenwald (3) in 1923, arteriosclerosis was present in 12, acute infections such as typhoid, pneumonia and osteomyelitis apparently were responsible in 18, trauma in 8 and syphilis in 7. The same seems to be true of splenic artery aneurysms. Trauma, acute infections and arteriosclerosis play a greater role than syphilis in the causation.

Renal artery aneurysm of the type reported above is usually a pathological curiosity. It is of arteriosclerotic

origin, frequently calcified, does not erode and rarely ruptures. It is usually unattended by symptoms except that it may occasionally be responsible for infarcts of the kidney. As in the present instance it may be discovered incidentally by a roentgen-ray examination. It is questionable whether under such circumstances the patient should be subjected to operation. If the condition of the patient is good operation might be attempted, but if not the aneurysm in itself is no more dangerous than in other portions of the diseased vascular system.

A case similar to this one was reported recently by S nderlund (4). A woman of 61, had symptoms of colon pyelitis for 2 years. The condition had grown worse with recurring attacks of stitch-like pain in the region of the left kidney. Cystoscopic examination showed slight cystitis. Colon bacilli and pus were found in the urine. The roentgen-ray showed a ring-shaped stone shadow, about half the size of a walnut, in the hilus region of the left kidney and calcific deposit in the wall of the aorta. It was proved by pyelography that the shadow was outside of the renal pelvis but very close to it. The correct diagnosis of calcified aneurysm of the renal artery was made. (A previous case had been studied in the same hospital several years before.) The diagnosis was supported by attacks of pain in the left kidney region which were interpreted as due to infarcts. Nephrectomy was performed. A calcified true aneurysm, 15x12 mms. in size and containing a thin layer of thrombotic material, was found on the upper main branch of the renal artery together

with several small infarcts of the kidney. The patient was discharged in good condition.

This seems to be the first case in which the diagnosis was made prior to operation or section. The diagnosis was made possible by a consideration of the following points:—

1. The likeness of the X-ray to the previous case studied in the same hospital.

2. The marked arteriosclerosis of the patient with calcific deposits in the abdominal aorta.

3. Stitch-like pain interpreted as due to infarcts of the kidney.

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## The Value of Scholarship\*

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SIXTEEN years ago I graduated in medicine and am returning tonight to acknowledge my great obligation to the Medical Department of the University of Buffalo.

You may remember that when Dante and his companion had climbed, with considerable toil, up the Mountain of Purgatory they approached a wide and pleasant looking terrace encircling the hill and being tired they sat down to rest and Dante, looking back upon the steep ascent to the terrace upon which they rested, turned to his conductor and said, "All men like to look backward."

If one could dispassionately examine the period of preparation and the subsequent augmentation of his medical knowledge he would at least approach the subject in a frankly critical frame of mind for the sole purpose of evaluating what he considered most essential in the progressive development of his professional capacity. The physicists will tell you that action and reaction are always equal. In my own particular case the benefits that I have derived from studious application to the tenets and principles of my profession have been more than

the effort, concentration and intensity of study would seem to warrant.

In addition, my remarks may be taken as the confession of a comparatively young man engaged in the practice of surgery, one who has to some extent been disillusioned, but not unhappily, and who has played the game as he has found it and whose experience may not be without some value to those who are junior to him in experience.

It has been recorded that three men set forth in search of Truth. The first said, "I will go to seek it in the wisdom of others. There, if anywhere, it is to be found." So he ensconced himself in the alcoves of a great library and began to pore over the tomes of all the sages in all centuries. Years and years he delved thus. One day as an old man he abruptly closed the volumes spread about him. "They all contradict each other," said he. "There is no such thing as Truth." The second man said, "It is not in books but in the lives of my fellow men that I shall find Truth." So he went forth for the quest, through all the marts and byways of mankind. In a few years he returned wearing the cynic's sneer. The third man hesitated. Said he, "Before I go to seek Truth, I fancy it will be well that I should try to practice it myself." And

\*Delivered before the Epsilon Chapter of Alpha Omega Alpha Fraternity, Buffalo, New York.



in that endeavor he became so absorbed that he postponed his great quest, year after year, all his life long. As he lay upon his deathbed, he sighed deeply. "I vowed to seek for Truth," he murmured, "and I have broken my vow." And then, even as he raised his eyes, there stood before him a shining apparition of great beauty. "I am Truth," said the figure and smiled down upon him. And, as the man gazed in silent amazement, the voice continued, "Truly, you had no need to look for me, for you found me and I have been at your side since that day long ago when you chose to do rather than to seek."\* Your entire professional life will be one of action and it is essential that you live and act the truth.

The essence of science is change and its function progressive improvement. As we continue to add to our professional activities from day to day we undergo a successional development in our medical knowledge and skill. Each new endeavor in scholarship is a milestone marking the way and if we could survey these milestones with a sufficiently distant perspective they would seemingly make a continuous straight line of progress. We know this is not strictly true, for life is ever a circle in which the present hearkens back to the past. Michael Angelo in Longfellow's poem expressed the thought so eloquently and so beautifully:

What other things I hitherto have done  
Have fallen from me, are no longer mine;  
I have passed on beyond them, and have  
left them

\*Editorial, Collier's Weekly.

As milestones on the way. What lies before me,  
That is still mine, and while it is unfinished  
No one shall draw me from it, or persuade me  
By promises of ease, or wealth, or honor,  
Till I behold the finished dome uprise  
Complete, as now I see it in my thought.

The four years of study in the Medical School which culminated with the degree of M.D. were but a stage in the preparation. You and I were called upon to digest and assimilate a great many unrelated facts. These were combined with a variety of theories and it was by the mental capacity and practical turn of our minds that this information was made useful in its most efficient form. The mere acquisition of the knowledge of the undergraduate course would have possessed relatively little value if it were not closely identified with the recognition of the clinical manifestations of disease. To have passed your medical examinations as an honor man or to have obtained a cum laude degree would have been relatively unimportant if the scholarship which it represented had not been continuous. After all, the science of medicine changes and moves on to new things. Our conceptions of histo-pathology are changing from year to year. Our therapeutics is being rewritten. The door of surgery is ever opening wider and wider. It is essential that all of us undergo a continuous or periodic re-education in medical knowledge, and from time to time, by travel, by post-graduate work, by selective reading, evaluate our clinical information in terms of present day scientific knowledge.

A bright and capable young man

could undergo the most extensive preparation in surgical laboratories and hospitals and fail to be even a modest success as a scientific surgeon. A man may by technical imitation become an excellent operator or he may make rounds through the hospital wards and in a mechanical way apply the principles of medical practice. This implies that the practice of medicine or the specialties may be purely mechanical as distinguished from the art of medical practice. Some men are endowed by birth with qualities that eventually make them successful doctors. Many will acquire the clinical personality that will make successful practitioners. It will be given to a few to have, either by natural inheritance or by the peculiar coaptation of personal qualities, that particular something that represents the art of practice. The art will connote that the individual is a teacher and a trainer of young men. The actual amount of labor that any one of us can accomplish as represented by the numerical notation of operations, sick people that we have attended, or medical contributions throughout an active lifetime is obviously small, but to the teacher in medicine his contribution is represented by the sum total of the labors of his students. To be a teacher demands a solid foundation of well qualified scholarship, character, good health and much study. If I should select an epigram as a descriptive caption for a teacher I should select the somewhat paradoxical phrase "the joy of labor." When the divine fiat was given to mankind, "by the sweat of thy brow thou shalt labor," there was expressed the greatest panacea for unhappiness.

When man is truly happy he labors most diligently in the particular vocation to which he has applied himself.

I should like to believe that aside from the patients that have been benefited and lived longer in happiness and contentment by reason of my surgical ministrations, I was essentially a trainer of youth. I know that here and there throughout this country are former students of mine who have received a little more knowledge, whose paths have been made easier, the inspiration for service more adequately instilled, the necessary self-denial and fortitude encouraged and that from this personal contact there flows that contentment which comes from being a teacher. A good teacher is scholarship successfully applied. As the mechanism, mental and physical, that most contributed to scholarship I place first the value of being born with a good heredity and a strong vibrant body. While an infirm or weakened constitution may carry a superlatively fine brain the demands made upon you will almost without exception require a splendid physical equipment. I would place second the master word "Work." Work, not for what the labor actually and by itself produced but what flowed from its application. Luck and chance may contribute no small part in placing you at the most opportune time in a position of great personal and professional advantage, but the ability to seize, hold and accept these opportunities will be the result of a preparation which has been intensive, prolonged and oftentimes painful. The formula may be adduced that work creates the ability to visualize and accept opportunity.

The casual practice of medicine is not enough to enable the young practitioner to carry himself through life successfully. He must learn how to use his education, to apply what he has learned to the everyday experience of his practice and to translate his medical information into terms of diagnosis, therapeutics and prognosis. In the application of this information in clinical medicine, irrespective of his specialty, he will suffer many disappointments because diagnosis must ever remain somewhat inexact by reason of the fact that we are interpreting along with our clinical facts and symptoms a diseased psychology. In the orderly rearrangement of his knowledge with such additions as science contributes to medicine from time to time he will derive his pleasure and his maintenance. He will be fulfilling in a large way the dictum of Shaw that an individual is entitled to as much happiness as he creates and no other activity will yield him such a large measure of return as adequate scholarship in medicine.

To put your name to an immortal poem or manuscript is genius; to be in a political position to write a pardon is power; to have financial resources sufficient to make good a check is capital; to have an understanding of the tools and equipment of your profession is happiness.

We live happily or otherwise in an age and in a country where the materialistic phase of success receives adulation and incites more imitation than any other. The more delicate, refined or subtle tests of success, success in a spiritual sense, success in the adjustment of oneself to the world about

him, which appraises service rather than gain, success which recognizes self-denial is often placed secondary to great wealth and power. In the acquisition of money I do not believe one can model a really successful career as a doctor, and I think if one will calmly survey his own activities he will be apt to believe that success lies in the development of character and self-control through personal experience.

There is no nobler calling in the annals of human affairs than that of a true practitioner of medicine. He must play the game at all times, sometimes under the most disadvantageous of physical circumstances, and the worldly remuneration he receives is, as a rule, inadequate to his self-devotion and sacrifice, but he has the satisfaction that comes from the thought that he has devoted himself to a service that, irrespective of the financial and social remuneration he will derive, gives a larger measure of happiness than can come from any of the other more or less arbitrarily applied professions.

The mere acquisition of money to the majority of people is probably conceived as the most useful occupation for the employment of one's talents. Yet to have obtained an excess of money and to have contributed nothing in the upbuilding of your students or of your profession would be indeed but a shallow measure of success. It would be absurd to suppose that money has no place in the life of a successful doctor. While art may rear itself from the sordid, meagre environment of poverty, the successful practice of medicine demands that the phy-

sician shall be relieved from the harassment and pressing demands of financial worry.

It is doubtful if any of us, when we began our medical course, had a well-defined objective. We were probably wise enough for our day to assume that a moderate amount of labor would give us adequate financial stability and the various callings of our profession provide sufficient labor to maintain a fair degree of contentment. As we grow older and see the number of men who have, according to our own opinion, failed, we cannot help but recall Goethe's hard saying, "Death is nature's expert advice to get plenty of life."

It is wise that all of us should determine for ourselves the final objective of our endeavors. We must of necessity feel that the practice of medicine in some one of its specialties is, after all, our vocation. We should zealously strive to perfect ourselves in the fundamentals of our science. It is well not to be too fixed in one's idea as to the exact established boundaries of medicine. Medicine embraces so many sciences and has so many angles, is capable of being applied in so many ways, that neither opinionativeness nor obstinacy of practice should make us forget that a large number of men go through life unchanged by the orderly progression and extension of the boundaries of medicine. How often have all of us heard:

"The sad rhyme of the men who proudly  
clung to  
Their first fault and withered in their  
pride."

It is essential for a person to cultivate a hobby, and I think for a medical man the cultivation of some type of literary pursuit, aside from one's reading in medicine, is the most profitable hobby or avocation that one can have. It requires but a little time, conscientiously given day after day, to acquaint oneself with the best and most splendid things in this world of ours, and no profession should be so crowded or the exigencies of practice so exacting that it does not permit time for the dreams that precede action.

"Books are the tools of the mind. Their function is to increase the treasures of wisdom and knowledge. In a very high sense they are the true labor-saving devices. What the loom does for the fingers, what the engine does for the feet, what the telescope does for the eye, that and more, books do for reason and memory. They hasten man's intellectual steps, they push back the intellectual horizon, they increase the range of his vision, they sow intellectual harvests otherwise impossible, and they reap treasures quite beyond the reach of the unaided reason."\*

\*Newell Dwight Hillis, in the *Watchman-Examiner*.

# Editorial

## Tobacco and Physical Efficiency

THE Committee to Study the Tobacco Problem published in 1923 Professor O'Shea's book on "Tobacco and Mental Efficiency," and in 1924 Professor Clark L. Hull's monograph on "The Influence of Tobacco Smoking on Mental and Motor Efficiency". In addition to these publications a number of laboratory studies have been published independently. The author of the present work just brought out under the auspices of the Committee is Dr. Pierre Schrumpf-Pierron, Professor of Clinical Medicine, University of Cairo, Egypt. There is a preface by Henri Vaquez, the noted Professor of Medicine, University of Paris. The members of the Committee, fifty-two in number, are well-known physiologists, internists, psychologists, pharmacologists, cardiologists, hygienists, geneticists, physical educators, economists, medical directors of life insurance companies and others. Alexander Lambert is President of the Committee. The publications of this body are presented in an unbiased manner, and the variations of opinions offered are those of the author or investigator, the committee itself expressing no opinion of its own as to the effects of tobacco on the animal organism. It has not attempted to give the results of original scientific investigations of its own, but presents a succinct survey of the literature, accompanied

by an extensive annotated bibliography. There is a very great mass of clinical material bearing upon the physical affects of tobacco, but it is widely scattered and much of it inaccessible. It has been very difficult for any one interested in the medical study of tobacco to get at this material, and there exists no medical compilation or analysis of clinical observations or studies along this line. Most of the lay writings about tobacco are prejudiced one way or the other, and very few physicians when pressed for definite statements as to the effects of tobacco upon the body are able to make any satisfactory statement. The problem is very much more difficult than in the case of alcohol, and various medical committees, notably that of Great Britain, have collected and analyzed the facts as to the effects of alcohol, and have made concise statements regarding these, accessible to every one. The pathological effects of tobacco, on the other hand, are not so apparent, and there is much greater opportunity for differences of opinion. There is much active propaganda for and against tobacco; both sides need the facts, and the subject needs thorough investigation and discussion. This book presents very complete data of all that is known about the action of tobacco by scientific investigation and observation up to the present time. The various chapters

cite the bibliographic references, state the nature of the investigation and its results, and give a brief summary of the total evidence offered. It is an unbiased and truthful discussion of one of the important problems of the day. The collective evidence as to the effects of tobacco as summarized in this volume are as follows. The chief poison in tobacco plant leaves is nicotin. In considering the toxicity of tobacco, however, the combined effect of nicotin and other components formed in the process of fermentation or due to combustion must be taken into account. Among these the first in importance are pyridin, ammonia and collidin. Prussic acid, carbon monoxide, pycolin, the phenols, etc., have but a secondary and perhaps negligible effect. Acute tobacco poisoning is due mainly to the effects of nicotin, although pyridin and other toxic constituents may have some influence. It is characterized by pallor, dizziness, faintness, sweating, palpitation, muscular weakness and collapse. Nicotin first stimulates and then powerfully depresses both the sympathetic and the parasympathetic ganglia of the autonomic nervous system; it also stimulates and then depresses the central nervous system, and the endings of the motor nerves in voluntary muscles. When injected into the circulation nicotin first causes a transient elevation of blood pressure and slowing of the pulse. These effects are due to stimulation of the vasomotor center and ganglia. With large doses the secondary effects on the circulation are a fall of blood pressure and marked quickening of the pulse, due to depression of the peripheral vasomotor and cardio-

inhibitory mechanisms. Nicotin first stimulates and then depresses the respiratory center. Large doses produce nausea and vomiting, partly through peripheral action, but chiefly through stimulation of the medulla. Death has occurred from the use of 30 gms. of smoking tobacco and 12 gms. of snuff. According to Schmiedeberg the fatal dose of nicotin for a non-smoker is the quantity contained in two cigars of moderate size, provided they could be swallowed entirely. Tolerance is easily acquired and habitual users of tobacco may absorb comparatively enormous doses and may easily tolerate from 40-50 mgms. of nicotin per day. There is no complete and trustworthy work on the comparative toxicity of different kinds of tobacco. Measurements of the amount of nicotin retained in the smoker's mouth, swallowed or absorbed, show, according to Lehmann that from one gram of cigar, there is retained or absorbed from 0.3 to 0.8 mgm. of nicotin; from one gram of cigarette 0.4 to 0.5 mgm. will be retained. As to its action upon the central nervous system there is reason to believe that chronic poisoning may give rise to motor and sometimes sensory aplasia, hemiparesis, and hemianesthesia; ocular disturbances, such as retrobulbar neuritis, hemianopsia, floating specks, inequality of the pupils, sluggishness of the external muscles of the eye; disturbances of the cochleoves-tibular nerve and the auditory and olfactory nerves, and neuritis of the cerebral nerves (facial, trigeminal and hypoglossal). Neuralgias, both diffuse and isolated (brachial, occipital, sciatic,) true polyneuritis, and finally symptoms of motor irritation (trembl-

ings and twitchings) are also very frequent in tobacco users. Tobacco may also cause headache, migraine, vertigo, insomnia, mental depression and amnesia. The abuse of tobacco is the cause of many cardio-vascular neuroses and disturbances of heart rhythm. Secondly, it may bring on hypertrophy of the heart. There is a conflict of opinion as to its possible role in the causation of actual lesions of the heart or blood vessels. A verdict of "not proved" on this question must be given, but there seems to be unanimity of opinion as to the adverse effects of tobacco in cases with latent or active changes in the cardiovascular system. Upon the respiratory system the effect of nicotin in small doses is to excite the respiratory center, moderate doses first excite and then paralyze, while large doses immediately paralyze it, death taking place from suffocation. Smoker's chronic laryngitis and smoker's asthma are well known clinically. The symptoms of the latter, evidently due to incipient paralysis of the center, disappear when the patient ceases smoking. In the digestive tract chronic pharyngitis due to the irritation of the smoke is very common in smokers. Less important is the so-called smoker's dyspepsia. Hyperchlorhydria is common in heavy smokers, and achlorhydria in chewers. The digestive disturbances of smokers are of nervous origin due to irritation of the centers. No antiseptic action of tobacco smoke on the mouth cavity is produced; carious teeth appear to be more frequent in smokers than in non-smokers. It is curious that this report does not discuss the question of the relationship of smoking to lip cancer since this etiology

is being stressed so heavily at this time in England. Buccal cancer is noted, and the conclusions drawn from the literature are to the effect that the role of tobacco in its production has been exaggerated. The action of tobacco upon the genitourinary system is practically unknown, and various statements as to the relation of smoking to impotence, miscarriage, metrorrhagia, etc., rest upon a doubtful foundation. On the other hand, the effects upon women workers in unhygienic tobacco factories appear to be more definite. Bottstein believes that certain forms of pruritus are associated with the abuse of tobacco. The role of tobacco as an important secondary factor in syphilis, alcoholism, lead poisoning, etc., is well known. The effect of alcohol upon the nervous system is greatly intensified by the use of tobacco; this is also true of the cardiovascular system. The chronic use and abuse of tobacco is frequently a complicating factor in neurosyphilis. The psychological effects of nicotinism have been widely discussed. There appears to be a generally unfavorable reaction of smoking upon scholarship, and upon the general mental efficiency, the greatest losses being in the fields of imagery, perception and association. Nicotin does not stimulate the cerebral functions, the contrary is the case. Smokers who attribute to smoking an increase in their capacity for intellectual and physical work are subjects of auto-suggestion, or the increased cerebral circulation from increased heart frequency may seem to produce an increased mental activity. It is curious that heavy smokers do not like to smoke in the dark, and that few blind people smoke. During the

war it was often noted that heavy smokers on losing their sight as the result of a wound, ceased smoking after a few months. The purpose of this work of the Tobacco Committee has been to collect the recorded medical knowledge regarding the effect of tobacco upon the human organism. As the result of this attempt one is compelled to admit that from the scientific and clinical point of view the study of the action of tobacco, as is also that of alcohol, must be still regarded as incomplete. The problem is very much the same in regard to both alcohol and tobacco. A sound individual may bear what for him is moderate doses without injury, but these amounts may be harmful to the unsound or to other apparently sound individuals. The immoderate use of tobacco brings on

a series of disturbances which are at first functional, then organic, and some of these are of serious importance. Since the War, and the excessive use of cigarettes following it, these clinical disturbances have become much more important and more frequent. The cigarette habit leads readily to abuse, and the cigarette smoker usually consumes more tobacco in smoking cigarettes than in smoking cigars. Further, because of the frequent habit of inhalation of cigarette smoke an opportunity is offered for the greater absorption of toxic substances. It is highly desirable that carefully controlled laboratory and clinical studies be carried out regarding the effects of the prolonged moderate use of tobacco, as well as its free use.



## Abstracts

*An Experimental Study of Diathermy.* By CARL A. BINGER, M.D., and RONALD V. CHRISTIE, M.B., Ch.B. (*Journal of Exper. Med.*, October 1, 1927, pp. 571-600.)

In view of the increasing use of diathermy by practitioners as a therapeutic measure, and as we do not possess any very definite knowledge concerning its effects upon internal tissues and organs it is very essential that investigations along this line be conducted until we have as thorough knowledge as possible of the mode of action, effects and sequelae of this use of heat. Binger and Christie have attacked this problem, and have published so far three papers: I. The Measurement of Lung Temperature, II. The Conditions Necessary for the Production of Local Heat in the Lungs, III. The temperature of the Circulating Blood. They were led to a study of the bodily responses to high frequency currents as a preliminary to an investigation of the value of diathermy in pneumonia. The problem confronting them was to find out whether deep localized heat could actually be produced in the body. The heating effects of the diathermy current have for the most part been studied in non-living systems; a favorite experiment has been the coagulation of egg albumin, or the cooking of meat and potatoes. The living body is not a sausage, nor yet a tube filled with albumin water, but is a heterogeneous system composed of tissues with different specific conductivities and heat capacities. Thus far, it has not been definitely established either that deep local heat can be produced by the diathermy current, or indeed, that the current penetrates into the deeper tissues of the body. Evidence has been presented that the so-called "skin effect" is a factor in keeping the current near the surface of the body. Bethman and Crohn state that they found it extremely difficult in experiments on anesthetized dogs to raise the systemic temperature more than a few frac-

tions of a degree. The fact of the passage of current through tissue can best be established by proof of heat development in the tissue. That this heat may be quickly dissipated, and that it may be conveyed to the tissue from adjoining structures, are two complicating factors which need to be carefully controlled. Working upon anesthetized dogs the authors found that evidence was obtained to show that in normal animals the rectal temperature can be elevated by the passage of high frequency currents. During life the intraabdominal and intrathoracic temperatures can be increased only slightly above the rectal temperature. The lung temperature in the anesthetized dog normally was 0.3—0.4 below the rectal temperature. During the passage of diathermy currents of strengths equivalent to those used in therapy this relationship is reversed—the lung temperature exceeding the rectal temperature by about the same value. Immediately after death, the temperature rises abruptly in the deep tissues between the electrodes. For the measurements of deep temperature special thermocouples were devised by the investigators, and their method of preparation and mode of use are described. In their investigations of the conditions necessary for the production of local heat in the lungs, it seemed apparent that blood cooling is a more effective mechanism in removing heat from the lung than air cooling. Indeed, it is probable that the condition most needed for the production of local heat in the lung, by the passage of the diathermy current, is a partially or completely blocked circulation in the pulmonary and bronchial vessels. Prevention of the access of air to one lung, while its circulation is intact, results in little, if any, change in the rate of heating of the lung by the diathermy current. Occlusion of a main branch of the pulmonary artery during the

flow of the current results in a sudden rise in temperature in the lung where the artery has been occluded, with subsequent heating, however, at the original rate. Under these circumstances death of the animal is accompanied by a precipitous rise in the temperature of both lungs. When the pulmonary veins as well as the artery to one lung are ligated the circulation through bronchial vessels is also stopped. Diathermy then results in a local rise in temperature in the lung equivalent to that seen in the other lung after death. These experiments convinced the workers that the normal lung can be heated only slightly above the systemic temperature by the application of high frequency currents to a dog's thorax. Interference with the circulation of blood, however, provides the conditions necessary for local deep heating. The implication seems obvious that the circulating blood carries away the heat produced in the lung. Such an interpretation is in harmony with the physiology of heat distribution and heat regulation. It is probable that together with its many other equilibrating functions the blood is a fairly ideal medium for distribution and maintenance of a uniform temperature. Further evidence of the effective cooling of the lung during diathermy by the blood circulating through it is presented in their third paper. It can be estimated roughly, assuming a minute volume of blood flow through the lungs of 2.50 liters, and a rise of  $0.2^{\circ}\text{C}$  in arterial blood temperature above venous, that approximately half of a large calorie of heat is being removed from the lungs per minute. This is evidently sufficient to prevent any marked degree of local heating. In conclusion, these investigators have devised a method of measuring intravascular temperatures in anesthetized dogs. The temperature in the abdominal aorta is uniform throughout, and varies only with the systemic temperature. The temperature in the inferior vena cava rises as the thermocouple approaches the heart, reaching its maximum at about the level of the hepatic veins. Between the hepatic veins and the right chambers of the heart there is no further elevation in venous temperature. The temperature of the right heart blood normally exceeds that of the

left heart blood by  $0.05-0.2^{\circ}\text{C}$ . During the application of high frequency currents to the thorax, this relationship is reversed. This indicates that the lungs are being heated, but that the blood passing through the pulmonary vessels is removing the heat at approximately the rate of production.

*The Treatment of Hemorrhage in Peptic Ulcer.* By WALTER A. BASTENO, M.D. (New York State Journal of Medicine, 1927).

Hemorrhage from a peptic ulcer may be:

1. a slight oozing which appears merely as occult blood in the stools; 2. a larger hemorrhage which shows grossly in the stool but it not large enough to produce obvious symptoms of hemorrhage; 3. profuse hemorrhage accompanied by weakness, fainting, air hunger and anemia; 4. continuous or frequently recurrent small hemorrhage that gradually brings on a marked secondary anemia. Whether the ulcer is gastric or duodenal does not alter the medical treatment for hemorrhage. The therapeutic desiderata are stoppage of the bleeding, overcoming the effects of loss of blood, and the fore-stalling and prevention of hemorrhage. His summary of treatment in severe hemorrhage: 1. Have the patient very quiet, lying down with head low, with plenty of fresh air and with body kept warm.

2. If there is severe exsanguination, bandage legs and arms, raise the foot off the bed, and bandage and put weights on the abdomen.

3. Avoid unnecessary manipulation of the abdomen.

4. Give a hypodermic of morphine sulphate 0.015 grm. (gr.  $\frac{1}{4}$ ) with strychnine sulphate 0.002-0.003 gram. (gr.  $\frac{1}{30}-\frac{1}{20}$ ).

5. Administer hypodermically every six to 12 hours 20 c.c. of fresh rabbit or horse serum 2 c.c. of hemostatic serum or 10 c.c. of thromboplastin.

6. Prepare early for transfusion and as soon as there are indications for it transfuse.

7. If there is exsanguination to the danger point and transfusion cannot be done, give intravenously Locke's or Ringer's solution, normal saline or 20 per cent glucose, and

give normal saline by rectum or by hypodermoclysis.

8. If the stomach remains distended and the bleeding seems to persist, lavage with tepid water and follow this by passing in through the tube a solution of thermoplastin, kephalin or gelatin with epinephrin. In cases with portal congestion, or if the bleeding has apparently ceased, avoid lavage.

When these measures are unavailing and dangerous bleeding persists, as shown by repeated vomiting of fresh blood or profuse bloody diarrhea, resort to surgery.

In cases with continued or repeated slow bleeding sufficient to produce a decided anemia but without immediate danger to life, the failure of medical measures calls for surgical intervention.

Subsequent treatment consists of total abstinence from stomach feeding and drinking for three days, giving saline by rectum every six hours to allay thirst. Give soap suds enema once a day. At the end of three days give milk of magnesia sufficient to clear out all remaining blood from the bowels. Then begin the regular medical treatment for ulcer. Have patient use bed pan for several days after the hemorrhage, and then a commode by the bed.

*Chloroma, The Recent Literature and a Case Report.* DORSEY BRANNAN (Bulletin of the Johns Hopkins Hospital, March, 1926).

The author reports a case of chloroma occurring in a white male child of fourteen years of age, whose chief complaint was paralysis of the left side of the face, beginning with pain in the ears; followed later by frontal headaches and vertigo. Diplopia soon developed, and vision of the left eye became impaired. His hearing had been poor for some time, and finally his ability to hear was almost lost. There was a swelling on the left temple. Pain over the mastoids developed. Slight exophthalmos was noted. White blood cells 36,800, myeloblasts 86 to 94.5 per cent. He was poorly nourished, and anemic. Bleeding from the gums developed, and the boy became gradually weaker, cachectic and more anemic. The head became unusually large and asymmetrical, resembling somewhat that of a hydrocephalic. Head-

aches were so severe that he often cried out with pain. The spleen became palpable a month before death. The lymph nodes of the posterior cervical chains, as well as a few axillary and inguinal nodes were enlarged. Pulse rate was usually rapid, and there was an irregular moderate fever. Death took place five months and twenty-six days after admission, ten months after the onset symptoms. The autopsy showed flat, irregular and hard tumor masses, most marked on the left side, scattered over the head. Marked exophthalmos, greater on the left side. Lymph nodes of the posterior cervical triangles, right axilla and in the groin were slightly enlarged, firm and movable. The autopsy findings of extensive green tumors over the skull, in the dura, parabasal sinuses, orbits, along the spine, sacrum and ribs in relation especially with the ligamentous structures and periosteum were distinctive enough of chloroma. Erosion of the bones and pressure atrophy of the tissues by tumor masses and infiltrating cells were well marked. The bone marrow was red and very abundant especially in the femur, but the examination was not extensive enough to exclude possible green patches. The slightly enlarged and firm spleen, the pale yellowish green and enlarged lymph nodes, renal and testicular masses and greenish discoloration of the supporting tissues constituted other but no less important pathological findings. The autopsy findings easily explain the symptomatology. Microscopically the tumors, bone marrow, organs and the blood cells showed the same large non-granular mononuclear cells, the myeloblasts, with few or many eosinophilic and a few neutrophilic myelocytes and polymorphonuclear leucocytes were absent. The infiltration of the organs was essentially the same as that in myelogenous leukemia. The large number of eosinophilic myeloid cells in the lymph nodes and in the edges of the orchitic tumor show the fallacy of associating the green color with these cells. The accumulation of the tumor cells within the lung alveoli was a peculiar feature, but it

has been observed before. The mitoses found were not especially atypical and tumor giant cells were not found. Megalokaryocytes were found only in the marrow. The pathological and clinical findings in this case prove it to be one of chloroma of myelogenous leukemia. This agrees with the better studied cases of chloroma during the last twenty years; they have all been regarded as myelogenous; only, the older cases and recent ones not well studied have been regarded as lymphoid in origin. Many authors have considered, or at least called, all large non-granular, mononuclear cells as lymphocytes, even in the presence of a fair number of myelocytes. Nevertheless, the bone-marrow origin of these cells was recognized more than twenty years ago, and they were called bone-marrow lymphocytes representing predecessor stages of myeloblasts. (This was clearly shown by Warthin in 1904, who was the first to regard *Chloroma as a tumor-like hyperplasia of the parent cells of the leucocytes, primary in the red marrow, the perosteum being involved only secondarily. As a result of this leucoblastic hyperplasia atypical leucocytes or leucocytes corresponding to some one of the normal types may appear in the circulating blood in varying numbers.* Chloroma may be leukemic or aleukemic.

The present case and all other carefully studied cases since 1904 have borne out the correctness of Warthin's views.) The author concludes that chloroma or chloroleukemia is a myelogenous process, an unusual form of myelogenous leukemia. Aleukemic stages of chloroma are common but true aleukemic forms of the disease are rare. Transitional or border-line and atypical cases occur, which emphasize the close relationship between myelogenous leukemia and chloroma. Nothing new is added to our knowledge of chloroma by this case report; it is only confirmatory of views expressed twenty-four years ago. Nothing new in regard to the green color is given. The writer thinks it probable that this is bound up with the myeloid cells. The peroxidase test was employed in this case in the study of the blood smears and of frozen sections of formalin preserved spleen, dural and cranial tumors, and in each case the reaction was strongly positive. At the present time there is no proof that any case of chloroma is of lymphoid origin, even though the cells in large proportion may superficially resemble lymphocytes. The writer also accepts the neoplastic properties of true chloroma, and regards this point as giving strong evidence of the neoplastic nature of leukemia in general.

## Reviews

*Physiology and Biochemistry in Modern Medicine.* By J. J. R. MACLEOD, M.B., LL.D. (Aberd.), D.Sc. (Tor.), F.R.S., Professor of Physiology in the University of Toronto, Toronto, Canada; formerly Professor of Physiology in the Western Reserve University, Cleveland, Ohio. Assisted by Roy G. Pearce, A. C. Redfield, N. B. Taylor, and J. M. D. Olmsted and By Others. Fifth Edition. 1054 pages, 291 illustrations including 9 colored plates. C. V. Mosby Company, St. Louis, Missouri, 1926. Price in cloth, \$11.00.

The fifth edition of this work has been expanded to meet the needs of medical students as a text book of physiology. At the suggestion of various teachers of physiology a section on the physiology of the special senses has been added by Dr. J. M. D. Olmsted, and the section on the neuromuscular system has been expanded by Dr. A. C. Redfield so as to include that part of the subject styled nerve-muscle physiology. The other portions of the volume have been thoroughly revised, and many chapters, such as those on blood, respiration, ductless glands, and the metabolism of the carbohydrates, have been practically re-written to bring the subject matter in line with recent advances relating to these subjects. The book still retains its original purpose of serving as a guide to the application of the truths of physiology in the bedside study of disease. It, therefore, is of value to the clinician, as well as to the medical student. It is, of course, increasingly difficult to present within the confines of a single volume a complete account of the rapidly expanding science of physiology in its correct relationship to previous knowledge, but an attempt has been made through the revision of every chapter to present the reader with at least a fair survey of the science of physi-

ology as it stands today. An examination of the subject matter of the book, to see if it bears out the success of their attempt, shows that it has been very successful in great part, but less satisfactory as far as some subjects are concerned. Particularly well brought up to date are the chapters of the respiration. Gesell's theory that the chemical control of respiration is the hydrogen-ion concentration of the respiratory center is clearly presented, and the author believes that this theory satisfactorily brings into harmony all the previous discordant hypotheses relating to the mechanism. Part VI on the respiration is one of the most up to date and best written portions of the book. Part V, on the circulation, is also very well done. That on digestion is much less satisfactory, particularly the portions relating to liver functions and the bile. A more detailed critical review of the large mass of work recently published upon this subject would be of great aid to practitioner and student. Naturally the chapters on carbohydrate and fat metabolism are thoroughly up to the moment and very satisfactory. Among the less satisfactory portions of the book are the chapters on lymph-formation and edema, renal function, shock, and the endocrinal glands. A wider knowledge of pathology would have helped all of these sections. There is also the usual omission of any section on the physiology of reproduction. Why do physiologists continue with this pre-Victorian silence on this most of all important function?

*A Text-book of Pathology.* By FRANCIS DELAFIELD, M.D., LL.D., Sometime Professor of the Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York; and T. Mitchell Prudden, M.D., LL.D., Sometime Professor of Pathology, College of Physicians and Surgeons, Columbia University, New

York. Fourteenth Edition. Revised by Francis Carter Wood, M.D., Director of the Pathological Department, St. Luke's Hospital, New York, Director of the Institute of Cancer Research, Columbia University, New York. 1339 pages, 20 full-page plates and 830 illustrations in the text in block and colors. William Wood and Company, New York. 1927. Price in cloth, \$11.00.

In the preparation of the manuscript for this, the fourteenth edition, of this well-known textbook on pathology the revising editor has endeavored to add to the text some of the more important developments in the subject of pathology which have appeared in the last few years. Aside from many detailed changes, especially new bibliographic references, the question of vitamins and hormones has been touched upon, changes have been made in the chapters on diseases of the thyroid, pancreas, lungs and blood; and a consideration of some modifications of certain lesions of the liver and gall-bladder have also been included. Additional matter has been inserted in the chapters on infectious diseases, pathology of the bones and joints, and nervous system. A considerable number of new illustrations has been added. The chapter on lesions following various types of poisoning has been eliminated, as these matters are covered much more fully and satisfactorily in the standard works on legal medicine than is possible in a textbook on pathology for students. The chapter on the preservation and staining of pathological tissues has also been omitted. The author would have been wise to have followed his own inclination and have excluded Part III, on the methods of making post-mortem examinations, since it is no longer practical or expedient to include post mortem methods, histologic technique and legal medicine in any textbook on general pathology, as they are in themselves sufficiently large in field and important enough to demand separate treatment, and the field of general pathology is so large that its satisfactory treatment needs the space accorded these other subjects. Also, it is no longer possible to treat in any adequate manner the sub-

jects of General and Special Pathology within the confines of one volume. This new edition is again handicapped from the start in the effort to do this, and the result is unsatisfactory. General pathology demands a broad treatment from the standpoint of general biology, and its satisfactory presentation would require a volume of the size of the present one. Special pathology suffers similarly; in this volume the space allotted to it is wholly insufficient. Although this fourteenth edition is a great improvement over the preceding, it still represents a transition stage between the pathological text-book of the late nineties and the modern conception of a teaching text-book of pathology. It is very difficult to insert new material satisfactorily into old. The patches also show their difference in texture and color, and that defect is very clearly evident in this edition. As it stands it is not a modern text book, thoroughly up to the moment.

*Fistula of the Anus and Rectum.* By CHARLES JOHN DRUECK, M.D., F.A.C.S., Professor of Rectal Diseases in the Post Graduate Hospital and Medical School, Chicago. 318 pages, 66 original illustrations. F. A. Davis Company, Philadelphia. 1927. Price in cloth, \$3.50.

As the author points out in his preface, every general practitioner of medicine is called upon to advise or treat patients suffering from rectal fistulae and many times, if not usually, finds himself confronted by a confusing array of symptoms and conditions with which he feels unable to cope. As a rule little attention is paid in the clinics of our medical schools to this great class of conditions which are by no means infrequent, but on the contrary, constitute a very common class of complaints in the public at large. Because of the numerous and diversified opinions as to the cause and manner of treatment by different authorities, the average physician meets a patient with rectal fistula with some hesitation and trepidation. As a result, improper treatment and imperfect operation are the rule, and most patients, diagnosed as anal or rectal fistula cases, become chronic patients whose end-results are usually

worse than their first condition. Drucek has gathered together the anatomical pathological, physiological and clinical knowledge gathered through years of study of a large number of individuals, who, suffering from fistulae, were required to submit to more than one surgical operation, and even then, many of them were obliged to go uncomfortably through life. In the treatment of fistulae the surgeon must never forget that the technical procedures incident to the removal of the fistula are only the first steps in the treatment, and that he must always preserve the functions of the rectum and anus. In a region, the anatomy of which is so intricate as is that of the perineum, with its many nerve trunks, its multiple muscles, tendons and fasciae acting in different planes, its peculiarly arranged blood supply, the preservation of function presents a very complicated problem, and emphasizes the need of delicate surgical procedures, vigilant postoperative care and subsequent physiotherapeutic measures. The greater part of the volume is directed to diagnosis and to treatment. These chapters are very well written, and the subject well covered and clearly presented. The illustrations are well chosen and are very good in representing the various conditions described. The printing is excellent and there are very few errors. The book can be recommended to the general practitioner as the best and most practical monograph on this subject.

*The Evolution of the Tubercle.* BY ALLEN K. KRAUSE, M.D., Associate Professor of Medicine and Director Kenneth Dows Laboratories, Johns Hopkins University, Baltimore. 95 pages. Journal of the Outdoor Life, 370 Seventh Avenue, New York. 1927. Price in cloth, \$1.00.

The text of this little book was prepared as an address on the research subject "The Anatomical Structure of Tubercle from Histogenesis to Cavity", which was delivered at the Fifth Conference of the International Union against Tuberculosis, Washington, D. C., on October 1, 1926. The author uses "tubercle" in the sense of all anatomical responses to tubercle bacilli, nodular or non-

nodular. He traces the development of characteristic forms throughout their evolution and attempts to answer why is *tubercle* the bodily response to tubercle bacilli, how does tubercle behave toward tubercle bacilli, and how does it behave toward the body? He conceives tubercle as of two types—nodular and non-nodular, and gives a morphological description of the origin and early evolution of primary nodular tubercle, and its minute structure. He regards nodular tubercle as representing the native anatomical response of the tissues to tubercle bacilli and non-nodular tubercle as representing a newly acquired allergic anatomical response to tubercle bacilli. In other words his use of the term tubercle is broadly synonymous with tuberculosis, anatomically considered, denoting every kind of formation, nodular, diffuse inflammation, suppurations and effusions of varied kinds, evoked by tubercle bacilli. Using the author's own recapitulation will perhaps give his conception more clearly. Briefly, there are microorganisms, tubercle bacilli, which can live and multiply in the human body, sluggish in development, but hardy of constitution and tenacious of life. Their hardihood and resistance to outside agencies is explained as due to their containing a high content of lipid substances in the form of a very refractory wax. When living, they settle in the body for the first time, the tissues react to their presence by forming nodular tubercle because they react in this way to the lipoids of the bacilli, the tubercle in effect being a foreign-body reaction serving to protect by walling off tubercle bacilli from normal tissue. Nodular tubercle is a circumscribed process evolving slowly out of the proliferation of cells *in situ*. With the presence of tubercle bacilli in the body, as represented by the establishment of nodular tubercle, the tissues acquire a new and added method of reacting to tubercle bacilli; a reaction to the *proteins* of the tubercle bacilli in the form of tissue *allergy* or *tissue hypersensitiveness*, the *allergic reaction*. This reaction brings about non-nodular diffuse tissue changes characterized by a rapid exudation of cellular elements from the blood to form acute inflammations and effusions. At bottom, tissue

allergy is also a defensive and conservative process. Tuberculous formations may be looked upon as composites of the effects of the lipoids and proteins of the micro-organisms concerned. The first stage, the tubercle, is a foreign body reaction to the lipoids, the allergic reaction a response to the dissociated proteins (tuberculins) derived from tubercle bacilli. Necrosis and fibrosis he regards as sequelae to the allergic acute inflammation of the second phase. The disease tuberculosis is based upon the extension and progression and repetition of tuberculous formations. The essential difference between the disease tuberculosis caused by living bacilli, and a state of tuberculous formations set up by dead bacilli is to be found in the capacity of indefinite and continued development and multiplication of tubercle inherent in living bacilli. In their normal evolution all tuberculous structures come to represent a mixture, in varying proportions, of the effects of nodular tubercle-formation and allergic inflammatory reaction. The ultimate issue of every tuberculous focus turns upon the balance struck between central necrosis and peripheral fibrosis. Necrosis of tubercle is a result of allergy—a sequel of the inflammatory reaction. It begins centrally and extends outward. Fibrosis is brought about through the conversion of epithelial cells of nodular tubercle into fibroblastic types. It is greatly enhanced by the allergic reaction as the latter subsides. It begins at the periphery and extends inward. It is unfortunate that the author has used tubercle as a synonym for tuberculosis, since the essential facts as presented here are concerned with the development of nodular tubercle and its later allergic phenomena. It is evident that this book was written without a broad knowledge of the pathology of tuberculosis. The writer appears to have no knowledge of the essential necrotizing action of tubercle bacilli upon the tissues and cells preceding the development of the foreign-body tubercle. There are many forms of tuberculosis in which the lesion is a local primary coagulation or *caseous necrosis* and in which the foreign-body tubercle never forms and there is no succeeding allergic inflammation or fibrosis. The lecture is written from a too

narrow experimental standpoint, and concerns the development of the *local nodular tubercle and its allergic phenomena* alone. It ignores wholly the *primary tissue lesion* produced by the action of living tubercle bacilli within the body, of which there is sufficient pathologic evidence.

*Medico-Legal Injuries.* By ARCHIBALD McKENDRICK, F. R. C. S., Ed., Medical Referee under the Workmen's Compensation Act; Consulting Radiologist to Edinburgh Royal Infirmary. 341 pages, 65 figures. Edwin Arnold and Co., London, England and Longmans, Green and Co., New York, 1927. Price in cloth, \$7.00.

This book was written as the result of a suggestion that an outline regarding accidental injuries, treated in as simple and non-technical manner as possible, to bridge the gulf between the non-medical mind and the highly technical terminology used in the ordinary medical text-books, would be of great assistance to those concerned in dealing with claims for compensation or damages in respect of injuries. It was not an easy task to accomplish this because of the inability to realize to what extent persons outside the medical profession appreciate or fail to appreciate medical terminology, methods of stating problems and drawing conclusions from them. The author has endeavored to make the treatment of each subject as self-contained as possible and this has involved a certain amount of repetition. There are seventeen chapters and three appendices. The chapters treat successively of an introduction to anatomy, the physics of injury, bone and joint injuries in general, regional bone and joint injuries, treatment and after-treatment of fractures and dislocations, back injuries, head injuries, the nervous system and how it works, pain, shock, heart strain, aortic aneurism, rupture of internal organs, accident as a cause of hernia, relationship of disease and injury, rheumatoid arthritis, and bacteriology. The three appendices are devoted to reflexes, guide to nerve supply of muscles of limbs and a glossary of terms. Naturally the chapter on anatomy is exceedingly elementary; that on the physics of injury is good, as are also the next five chap-



ters on various injuries of bones and joints, back and head. The different forms are described in simple language, and the accompanying illustrations serve their purpose. The remaining chapters are too elementary, and there are many important omissions. Fat embolism following trauma receives no consideration, and this is surely one of the most important medico-legal points to be considered in death following bone injuries. Its symptoms are not differentiated from those of shock. Embolism in general is not treated, nor is thrombosis. Neither one is mentioned in the index. A whole chapter is given to rheumatoid arthritis, which the author regards as the third foot of the tri-

pod upon which so many medico-legal claims are founded, the other two being traumatic neurasthenia and shock. American physicians concerned in accident insurance and compensation work will hardly agree to this sweeping statement. One of the most frequently raised questions in the United States in this work is the relationship of trauma to neoplasm, and this important question receives no attention. There is also no consideration of electrical injuries which are so common with us. While this little volume has much of value in it, it is a matter for regret that so much of vital importance has been omitted. It may be recommended for what it does contain.

## College News Notes

A good illustration of the activity of Fellows of The College in contributing to medical literature may be taken from the October 22, 1927 issue of The Journal of the American Medical Association. Seven Fellows of The College are contributors to this one issue of The Journal.

Dr. O. H. Perry Pepper, Philadelphia—Hematology of Subacute Streptococcus Viridans Endocarditis.

Dr. John Phillips and Dr. J. P. Anderson, Cleveland—Cardiac Disturbances in Goiter.

Dr. Glenville Giddings, Atlanta—Friedreich's Ataxia in Ten Members of a Family.

Dr. A. F. R. Andresen, Brooklyn—Treatment of Gastric Hemorrhage.

Dr. Kennon Dunham, Cincinnati—The Diagnosis of Tuberculosis in the Child's Chest.

Dr. Julius H. Hess (with Dr. I. McKy Chamberlain), Chicago—Gelatin Added to the Diets of Artificially Fed Infants.

Announcement is made of the appointment by President Smithies of Dr. Clarence Manning Grigsby, 424 Wilson Building, Dallas, Texas, as Governor for the State of Texas to fill the unexpired term of Dr. Kenneth M. Lynch who has presented his resignation due to his permanent removal from that State. Dr. Grigsby is Professor of Theory and Practice of Medicine at Baylor University Medical Department, and is an outstanding man in his State.

### OBITUARY

*Dr. Peder A. Hoff, St. Paul Minn.*

Died during September of heart disease, after a brief illness; aged 57.

Following his graduation from the University of Minnesota Medical School in 1900, Dr. Hoff took a postgraduate course in internal medicine at the Harvard Medical School, and later pursued further post-graduate study at the University of Vienna. He was instructor of medicine at the University

of Minnesota Medical School from 1902 to 1914, Visiting physician to the City Free Dispensary 1902 to 1914, a member of the visiting staff of the City and County Hospital 1902 to 1914. At the time of his death, he was staff physician to St. Luke's Hospital, consulting physician to the Northern Pacific Railway and chief medical examiner for the New York Life Insurance Company. During the World War, he held the commission of Lieutenant Commander in the United States Navy.

Several years ago he was elected to membership in the American Congress on Internal Medicine, and subsequently transferred to Associateship in The College. He was also a member of the Minnesota Medical Association, the Ramsey County Association and the American Medical Association.

*Dr. Joseph Howell Way, Waynesville, N. C.*

Died September 22 of heart disease, at Asheville; aged 61.

Dr. Way was graduated from Vanderbilt University School of Medicine in 1886. Since 1905 he was a member, and since 1911, president of the state board of health, member of the state board of medical examiners 1897 to 1902. During the World War Dr. Way served successively as captain, Major, lieutenant colonel and colonel, being assigned to Base Hospital at Camp Greene, the Rockefeller Institute and the U. S. A. School of Tuberculosis. At the time of his demise, he was colonel, Medical Reserve Corps, U. S. A.

Dr. Way was a member of many medical societies, having acted as president of the Medical Society of the State of North Carolina, past president, secretary and treasurer of the Tri-State Medical Association of the Carolinas and Virginia, member of the House of Delegates to the American Medical Association 1904-09, and in 1909 member of the Reference Committee on Sec-

tions and Section Work. He was elected a Fellow of The College December 12, 1925, and maintained a constant, loyal and helpful interest in its work.

#### PRELIMINARY PROGRAMME FOR NEW ORLEANS MEETING

Preliminary program of the American College of Physicians for the meeting in New Orleans next spring, beginning March 5. The meeting will start on Monday, at 10 A. M. with the usual address of welcome from the Mayor of New Orleans; the President of Tulane, Dr. Dinwiddie; The President of the Orleans Parish Medical Society and Dr. C. C. Bass, Dean of the School of Medicine of Tulane University of Louisiana. Dr. Frank Smithies will give a reply to the address of welcome. The program will be continued as follows:

1. Dr. Julius Bauer, Vienna, Austria. (Title to be announced).

2. Dr. David P. Barr, "Multiple Myeloma."

3. Dr. L. G. Rowntree and Dr. George E. Brown, "Studies in Blood Volume with the Dye Method."

4. Dr. Joseph Sailer. Title to be announced.

5. Dr. Frank R. Menne, "The Effect of Iodin on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

#### EVENING SESSION, MONDAY, 7:45

1. Dr. Maud Slye, "Cancer and Heredity."

2. Dr. J. L. Goforth, "Natural and Acquired Body Resistance to Neoplasia."

#### TUESDAY MORNING, MARCH 6—10 O'CLOCK

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."

2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."

3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."

4. Dr. C. C. Sturgis, Dr. Raphael Isaacs and Dr. Millard Smith: "Treatment of Pernicious Anemia with Liver Fraction."

#### Symposium on Tuberculosis.

5. Dr. Charles L. Minor. Title to be announced.

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

#### EVENING SESSION—7:45 O'CLOCK

1. Dr. James S. McLester. Title to be announced.

2. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

3. Dr. T. Z. Cason, "Some Unfinished Research Problems of the South."

#### WEDNESDAY MORNING, MARCH 7— 10 O'CLOCK

1. Dr. L. F. Bishop, "The Practice of Cardiology."

2. Dr. Morris H. Kahn, "Heart Strain and Its Consequences."

3. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

#### Symposium on Epilepsy

4. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

5. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

6. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

7. Dr. Tom Throckmorton. Title to be announced.

#### EVENING SESSION—7:45 O'CLOCK

#### Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."

4. Dr. J. C. Small, "Rheumatic Fever."

#### THURSDAY MORNING, MARCH 8—10 O'CLOCK

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."

2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."

3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the View Point of an Internist."

#### Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."

5. Dr. Frederick M. Allen, "Present Results and Outline of Jeaklic Treatment."

6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."

7. Dr. W. H. Olmstead, "The Dietetic Management of the Diabetic in the Doctor's Office."

#### FRIDAY MORNING, MARCH 9—10 o'CLOCK

##### Symposium on Tropical Medicine.

1. Colonel Roger Brooke. Title to be announced.

2. Dr. Aldo Castellani. Title to be announced.

3. Dr. Wm. M. Jones, "The Early Lesions of Intestinal Amebiasis."

4. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.

5. Dr. Aristides Agramonte, Havana Cuba. Title to be announced.

#### FRIDAY EVENING, MARCH 9—7:45 o'Clock

1. Dr. Julius Bauer, Vienna, Austria. Convocation Address.

The scientific program as given above will take about half of the time of the meeting. The remainder of the time will be occupied by clinics. In the afternoon from 1:45 to 4:30, clinics will be held at the Charity Hospital of New Orleans, Touro Infirmary, the Hutchinson Memorial, the Richardson Memorial, Hotel Dieu, the Baptist Hospital, Mercy and Presbyterian Hospitals. At the Charity and Touro Infirmary, the program will be changed in the middle of the week, so that two separate programs will be put on at these two hospitals. The same will apply to the program at the Hutchinson Memorial. Clinics will be given at the Charity Hospital by Dr. George Bel, Dr. J. B. Guthrie, Dr. Amadee Granger, Dr. A. E. Fossien, Dr. J.

L. Lewis, Dr. Randolph Lyons, Dr. J. H. Musser, Dr. Robert Bernhard, Dr. W. A. Love, Dr. George R. Herrmann, Dr. Philip Jones, and others. At the Charity Hospital, Dr. Julius Bauer, of Vienna, will give a clinic on certain days.

At the Touro Infirmary, clinics will be given by Dr. L. R. DeBuys and his staff and by Dr. I. I. Lemann and his staff. Dr. DeBuys' staff will limit themselves to diseases of children; Dr. Lemann and his staff to internal medicine and to subjects related to internal medicine more or less closely, so that it is quite possible with the present plan to have a surgeon to discuss cases in which the internist and the surgeon come into close contact, such as thyroid cases, abdominal conditions and so on.

At the Baptist Hospital, Dr. Oscar W. Bethea will run the program.

At Hotel Dieu, Dr. S. Chaille Jamison, Dr. Maurice Couret, Dr. L. A. Fortier and others will give clinics.

At the United States Marine Hospital, Dr. W. C. Rucker will be in charge of the program. There are always a large number of interesting tropical and unusual diseases at the Marine Hospital.

At the Hutchinson Memorial, clinics and demonstrations will be given daily. Dr. Wm. M. James and Dr. J. J. Vallarino, of Panama, will demonstrate their preparations and x-ray findings in amebiasis. Dr. J. C. Small, in addition to his scientific paper, will give in more detail than can be done at a large scientific meeting the particulars of the studies he has made in rheumatic fever. Dr. Robert S. Berghoff will give an afternoon demonstration on the diagnosis of chest diseases; Dr. T. J. Perkins, "Constitutional Type in Relation to Mental Disease;" Dr. Aldo Castellani, "Fungus Growth;" Dr. C. C. Bass, "Malaria;" Dr. F. M. Johns; Dr. H. W. Butler, "A Slide Method for the Diagnosis of Syphilis;" Dr. Roy H. Turner, "Intestinal Microbiology." A clinical pathological conference will be given one or two days.

The program at the Richardson Memorial will be under the supervision of Dr. J. A. Lanford, who has invited Dr. C. W. Duval,

Dr. Henry Laurens, Dr. Irving Hardesty and Dr. J. T. Halsey, Professors of Pathology, Physiology, Anatomy and Pharmacology, respectively, with their staffs, to demonstrate research problems that they are actively engaged in or which they recently completed.

#### REDUCED FARES

Twelfth Annual Clinical Session, New Orleans, La.

The Executive Secretary advises that all railroads of the United States and of eastern Canada have granted reduced fares to our Clinical Session on the Certificate Plan of fare and half fare. Those who attend the Session will purchase going ticket at local railroad office and at the same time request a "Certificate." This Certificate, when validated by the proper officers at the registration booth at New Orleans, will entitle attendant to purchase return ticket at half rate.

These reduced rates apply not only to the attendant, but to dependent members of his family.

Going tickets may be purchased from March 1 to 7, and the return ticket may be used up to March 13. For those who desire to remain in New Orleans longer, the return ticket may be used until March 24, upon deposit of Certificate with W. H. Howard, Special Agent located in the City Ticket Office of the Louisville and Nashville Railroad, New Orleans, upon payment of fee of \$1.00 per Certificate receipt at time of deposit.

The Executive Offices have on hand a number of old YEAR BOOKS, 1923-24. While these have no present value from the standpoint of directory purposes (the new 1927-28 Year Book was issued during the summer), they may be of interest and historical value to some of our members of more recent election. The Executive Secretary will gladly send a copy to any member upon receipt of 50c in stamps to cover cost of handling and mailing.

# Epilepsia Tarda\*

By DAVID RIESMAN, M.D., and THOMAS FITZ-HUGH, JR., A.M., M.D.,  
*Philadelphia, Pa.*

GENERALIZED convulsions occurring for the first time in adult life are not infrequently viewed as diagnostic of uremia or of some gross brain lesion. Such preconception, however, leads to many errors in diagnosis and prognosis.

It is our purpose to call attention anew to the recently somewhat neglected subject of so-called *epilepsia tarda* and to attempt an analysis based on our own experience and a review of the literature.

Great confusion exists concerning the meaning of the term *epilepsia tarda* (senile epilepsy). Some authors (1) (2) (3) would restrict it to those cases of "idiopathic epilepsy" of later life which present no evidence of cerebral arteriosclerosis or other organic disease. Others on the contrary—and this includes most of the modern writers—feel that senile epilepsy is in some way related to disturbances of the cerebral circulation incident to cerebral arteriosclerosis and atheroma. In surgical literature one finds "*epilepsia tarda*" designating cases of delayed Jacksonian convulsions due to prior cranial injury. Further confusion is

obvious from the statement of a widely used medical dictionary that "senile epilepsy is senile bradycardia coming on in paroxysms and resulting from coronary sclerosis....".

We would label with the term *epilepsia tarda* those patients who exhibit recurrent generalized epileptiform seizures after forty years of age and who fail to show any sufficient etiologic factor other than a background of circulatory inadequacy, with special reference to periodic insufficiency of the cerebral circulation.

This tentative definition commits us to the hypothesis that the convulsions of *epilepsia tarda* are initiated, in part at least, by moments of deranged cerebral circulation—the pre-existing background for which we believe is usually demonstrable. That there is another factor—the unknown X of all the forms of epilepsy must be admitted. An approach to this unknown, we feel, may be made possible through a study of the types of *epilepsia tarda* in which a knowable factor seems to operate.

Patients with *epilepsia tarda* as observed by us may be conveniently divided into groups as follows:

1. The arteriosclerotic group.
2. The hypertensive group.
3. The mixed hypertensive-arteriosclerotic group.

\*Read before the Association of American Physicians, Atlantic City, N. J. May 2 and 3, 1927.

4. The endocrine dysfunction group, including (a) diabetes mellitus, (b) dyspituitary and hypothyroid disorders.

5. The cardiac group, including (a) Adams-Stokes disease, (b) aortic stenosis, etc.

No cases of group five are included in the present report. Nor is any mention made of those allied conditions of transient paralysis and aphasia described by Osler (4), Riesman (5) and others. The convulsions of general paresis are also omitted in our report—although they too doubtless belong to the arteriosclerotic group of epilepsy tarda. As may be seen from the following case reports the groups are by no means sharply defined, but merge one into another.

#### CASE REPORTS

*Case No. I. (Arteriosclerotic Type)* Mrs. F. G.—Age 69. 11/6/25—Patient was well until two years ago when she fell unconscious on stairs and was found in a generalized convulsion. No cranial injury but arm was broken. Convulsion lasted several minutes; unconsciousness lasted an hour. Since then the patient has had ten attacks of unconsciousness with epileptiform seizures—three diurnal and seven nocturnal. No aura. She is dazed after consciousness returns and speech is thick but no residual paralyses have occurred. Recently she had two convulsions in one night. Incontinence of bladder and bowel in several attacks, but no tongue biting. Patient has had in addition two attacks of momentary unconsciousness without convulsions. Disposition becoming irritable; memory impaired; outbursts of causeless laughter recently. Some vertigo at times preceding the attacks and also without relation to attacks. Constipation always. Never had juvenile convulsions.

Examination: P.88; B. P. 150/60; W. 173. Ophthalmoscopic examination reveals

marked retinal angiosclerosis. Heart enlarged to left about 3 cm. and downward to 6th interspace in anterior axillary line. Occasional extrasystoles. Neurologic examination negative. Peripheral arteries hard. Urine: acid, 1012, no sugar, a trace of albumin, many pus cells, a few hyaline casts.

Summary diagnosis: (1) Epilepsia tarda (2) Arteriosclerosis (3) Cardiac hypertrophy with extrasystoles.

*Case No. II. (Arteriosclerotic Type)* Mr. W. H., negro—Age 55. 11/12/23—For the past year but never before patient has had about twelve generalized convulsions with unconsciousness and tongue biting and urinary incontinence. Attacks chiefly nocturnal. No aura. Nothing else of significance in history except occasional nocturia and bleeding hemorrhoids.

Examination: P.60 to 70; B.P. 120/70. Well developed negro. Marked retinal angiosclerosis but no demonstrable hardening of the peripheral arteries. Heart negative except for a blowing systolic murmur at the mitral area. Neurologic examination negative. Urinalysis negative. Blood and spinal fluid and Wasserman negative. Blood urea nitrogen, blood uric acid, blood sugar—all normal. Blood count moderate secondary anemia. Electrocardiogram shows sinus bradycardia.

Summary Diagnosis: (1) Epilepsia tarda. (2) Cerebral arteriosclerosis. (3) Secondary anemia from hemorrhoids. (4) Systolic cardiac murmur.

*Case No. III. (Arteriosclerotic Group)* —Mrs. R. P.—Age 74. 4/20/27—For the past year patient has had nocturnal convulsions every few weeks with stertorous breathing, swallowing movements and bladder incontinence. False teeth are removed at night and tongue is not injured by the biting which occurs. No aura. Some mental irritability. Constipation for years. No juvenile convulsions. No epilepsy in family.

Examination: Wt. 138; P. 92; B. P. 164/90. Peripheral arteries hard. Well marked ret-

inal angiosclerosis. Thyroidal adenoma. Heart enlarged with left border one inch beyond mid-clavicular line. No murmur. No arrhythmia. Urine: acid, 1015, albumin a trace, no sugar, a few hyaline and light granular casts.

Summary Diagnosis: (1) Epilepsia tarda. (2) Arteriosclerosis. (3) Cardiac hypertrophy.

*Case No. IV. (Hypertensive Type)*—Mrs. D. C.—Age 48. 11/24/26—Patient has known that her blood pressure was too high for the past eight years. In 1918 began to have headaches, vertigo, tinnitus and shortly thereafter had her first convulsion. From 1918 to 1924 she had repeated attacks of unconsciousness with generalized convulsions lasting from fifteen to twenty minutes and followed by mental dullness. Aura of "something rising up from epigastrium." No tongue biting or incontinence. Attacks all diurnal. No petit mal. Has had no attacks for two years. No juvenile convulsions. Patient also complains of gaseous indigestion and crying spells and constipation. Menopause three years ago at forty-five.

Examination: Overweight (159); B. P. 240/140; P. 104. Heart enlarged 2 cm. to left of mid-clavicular line. Area of supra-cardiac dullness increased. Aortic second sound accentuated. Tenderness over the gall-bladder area. Reflexes normal. No demonstrable arteriosclerosis. Urine: acid, 1020, albumin trace, sugar negative, microscopy negative. Blood urea nitrogen and blood sugar normal. Phenolsulphonephthalein elimination 45% in two hours.

Summary Diagnosis: (1) Epilepsia tarda. (2) Hypertension. (3) Gall bladder disease. (4) Cardiac enlargement. *Course*: Patient has been symptomatically improved by low salt low protein diet together with biliary drainage, acidophilus milk, and the use of bromides and luminal and colonic irrigations. Last examined 1/17/27—Wt. 157; B. P. 212/118. No more convulsions.

*Case No. V. (Mixed Arteriosclerotic Hypertensive type)*—Mr. E. H. Age 59. 9/15/25—For five years has had dyspnea on

exertion and edema of the feet. In September 1923 had his first convulsion and had recurrent convulsions with unconsciousness about once a month for the next year—always nocturnal and associated with tongue biting and bladder incontinence at times. Previous history includes gonorrhea and inflammatory rheumatism. No convulsions have occurred during the past year since his doctor (R. D. Anderson of Burlington, N. J.) began the use of luminal.

Examination: Overweight; P. 80; B. P. 180/100. Marked peripheral arteriosclerosis and retinal arteriosclerosis as well. Marked cardiac hypertrophy with engorged liver extending three inches below costal border and a blowing systolic mitral murmur. Some edema of legs and feet. Prostate markedly enlarged and urethral stricture reported by urologic examiner. Urine loaded with pus. Blood urea nitrogen 38—reduced to 18 by indwelling catheter. Blood Wassermann negative.

Summary Diagnosis: (1) Epilepsia tarda, (2) Arteriosclerosis and hypertension, (3) Cardiac hypertrophy with decompensation, (4) Prostatism. *Course*: The constant use of luminal in half-grain doses seems to have completely abolished convulsive seizures. He died 3/31/27 of cardiac decompensation and uremic (?) coma without convulsions or paralyses.

*Case No. VI. (Mixed Arteriosclerotic-Hypertensive type)*—Mr. M. H. Age 56. 11/7/22—Patient has had attacks of vertigo for the past year with occasional headache and palpitation.

Examination: B. P. 196/100; P. 84; Wt. 196. Patches of leukoplakia inside cheeks. Faint systolic murmur at aortic area and slight left-sided cardiac enlargement. Moderate edema of shins. Peripheral arteries moderately sclerosed. Arcus senilis present. Urinalysis: 1028, albumin trace, sugar negative, microscopy negative. Blood Wassermann negative.

12/14/22—Fell down stairs in a "dizzy spell." No witness and no knowledge of convulsion. 1923—Had broncho-pneumonia. Blood pressure tending higher. 3/24/26—



While on ocean trip from Bermuda (3/14/26) had sudden vertigo and lapsed into unconsciousness. Eye witnesses state that he had a violent convulsion with bloody froth from mouth. Vomited on regaining consciousness.

Examination: B. P. 210/110; Wt. 184; P. 76. Urine as before except more casts. Blood urea nitrogen, uric acid, sugar, and creatinin normal. B. S. P. 35% elimination in two hours. Electrocardiogram shows "severe myocardial degeneration." Ophthalmoscopic examination (Dr. Fewell) "marked angiosclerosis. No hemorrhages." 7/16/26—Generalized convulsion with tongue biting followed by visual hallucinations which lasted several weeks. 9/4/26—Convulsion preceded by aura of vertigo and precordial distress. Occasional extrasystoles noted after this attack. 3/7/27—Convulsion with severe laceration of the tongue. Blood pressure in the attack was over 300 mm., pulse was 120 and gallop rhythm developed with a grating systolic murmur over the entire heart. Patient passed sixty ounces of urine in the three hours following this attack. No sphincteric incontinence at any time. 4/10/27—Convulsion as above. A good deal of anginoid discomfort.

Summary Diagnosis: (1) Epilepsia tarda. (2) Hypertension and arteriosclerosis. (3) Myocarditis.

*Case No. VII.* (Mixed Hypertensive—Arteriosclerotic-luetic). Mr. W. B. T. Age 58. 2/2/24—For the past year patient has had recurrent generalized convulsions with unconsciousness, tongue biting and urinary incontinence. Most of the attacks are nocturnal and are frequently preceded by aura of precordial distress. Has been overweight for many years. Was first told he had high blood pressure two years ago. Chancre at twenty-one years of age. No juvenile convulsions. No epilepsy in family.

Examination: Wt. 202; B. P. 215/115; P. 80. Large and obese. Eye grounds show marked arteriosclerosis and small patch of choroiditis inside both discs. Neurologic examination negative except absent left knee jerk. Heart enlarged with left border at anterior axillary line. Rough systolic mur-

mur at aortic area transmitted to neck. Urine: 1020, no sugar, albumin a trace, a few granular casts. P. S. P. 50% in two hours. Blood Wassermann plus four.

Summary Diagnosis: (1) Epilepsia tarda. (2) Hypertension and arteriosclerosis. (3) Syphilitic aortitis and cardiac hypertrophy. *Course:* Patient improved under antisyphilitic treatment, dietary management and the use of luminal. Convulsions did not recur for full year when patient stopped treatment. Last heard from in March 1927. (act 61), he had suffered a right hemiplegia.

*Case No. VIII.* (Endocrine Dysfunction type: Diabetes Insipidus). Mrs. R. S. Age 53. 2/22/27—Patient was well until menopause at forty-six when she had vertigo and flushes and has not felt well since. A year ago she was told for the first time that she had high blood pressure. During the past month she has had two attacks of unconsciousness with jerking of the head and face and limbs but no tongue biting or incontinence. Attacks preceded by aura of choking feeling in throat and burning feeling in epigastrium and followed by dazed mentality for several hours. No nocturnal attacks. No petit mal. Ever since first attack has had very marked polydipsia and polyuria—passing five to six quarts of urine in twenty-four hours. Has become very nervous and memory is failing. No juvenile convulsions. Weighed 150 pounds at marriage and went up to 208 pounds a year ago. Comes of fat stock.

Examination: Wt. 197; P. 92; B. P. 170/80; "Full moon face." Lower eye lids puffy. Tonsils very large. Heart negative except for a soft systolic murmur at apex in recumbent posture. Abdomen adipose. No demonstrable arteriosclerosis. Neurologic examination, negative except knee jerks greatly diminished. Urine 1006, no sugar, no albumin. Blood Wassermann and Kahn tests negative. Blood sugar: .98% (fasting).

Summary Diagnosis: (1) Epilepsia tarda. (2) Diabetes insipidus. (3) Hypertension. (4) Heart murmur.

*Case No. IX.* (Endocrine Dysfunction type: Hypothyroidism. Arteriosclero-

sis). Mrs. J. M. Age 53. 12/20/21—Patient was well except for obesity and dyspnea on exertion until two months ago when she began to have convulsions of brief generalized type. Has had about fifteen such attacks in past two months. Following attacks she is confused and recently has been childish and forgetful. Has aura of precordial distress at times. In several of the attacks the tongue has been bitten slightly and the bladder has emptied incontinently. Always constipated.

Examination: B. P. 120/70; P. 100; Obese. Hair of scalp sparse and dry. Face and hands suggests myxedema. Ophthalmoscopic examination (Dr. Baer) "marked retinal angiosclerosis with a few recent hemorrhages around both discs." Heart enlarged 3 cm to left of mid-clavicular line. Sinus arrhythmia and tachycardia at times and at other times slow rate. Sounds muffled. Large umbilical hernia. Neurologic examination negative. Repeated urinalyses, blood counts, blood chemical examinations, blood Wassermann—all normal. Basal metabolism (during afebrile period when pulse rate was averaging about sixty-two) was minus 16%.

Summary Diagnosis: (1) Epilepsia tarda. (2) Arteriosclerosis. (3) Cardiac hypertrophy. (4) Hypothyroidism. *Course:* Treatment by rest in bed, low salt low caloric diet, and colonic irrigations together with bromides and thyroid extract was followed by a period of eleven months of marked improvement. The convulsions ceased and the mental condition cleared up entirely. Thirteen months after onset the patient had hemiplegia and died.

*Case No. X.* (Endocrine Dysfunction type—Diabetes Mellitus with Hypertension and Arteriosclerosis). Mr. W. P. Age 50. 11/15/26—Well until four years ago when he had right renal colic. Three years ago right nephrectomy for nephrolithiasis. Felt well until May 1926, when he had a convulsion which left him with some motor and visual aphasia but no other paralysis. Second convulsion today, 11/15/26, generalized with tongue biting and followed by a deep sleep lasting two hours.

Examination: Wt. 170; B. P. 250/140; P. 60. Eye-grounds show silver wire arteries indenting the somewhat dilated veins. No cranial nerve palsies. Heart slightly enlarged. Rough systolic murmur at aortic area and marked accentuation of second aortic sound. Reflexes normal. No edema. Blood urea nitrogen—28 mgms. per 100 cc, blood sugar 199 mgms. per 100 cc. Urine loaded with pus and containing 1% of sugar and a heavy trace of albumin. Specific gravity 1020. Urinary tract: X-ray shows several small calculi left kidney. Blood Wassermann negative.

Summary Diagnosis: (1) Epilepsia tarda. (2) Hypertension and Cardiac hypertrophy and aortitis and arteriosclerosis. (3) Diabetes Mellitus. (4) Nephrolithiasis. *Course:* 4/4/27—Under diabetic management blood sugar is normal. Urine is free of sugar and no more convulsions have occurred but hypertension, aphasia and pyuria persist.

*Case No. XI.* (Endocrine Dysfunction type: Diabetes Mellitus, Arteriosclerosis). Mrs. L. McL. Age 59. 11/2/22—Diabetes was discovered at the age of seventeen. After one year of treatment patient considered herself cured and apparently remained well for the next forty years when loss of weight, polyuria and polydipsia recurred and sugar was again found in the urine (1920). Soon after this patient began to have attacks of unconsciousness with convulsions (aet 57).

Examination: B. P. 100/70; P. 72; Wt. 95. Considerable emaciation. Marked peripheral arteriosclerosis. Heart enlarged with left border an inch beyond mid-clavicular line. Marked edema of legs. Neurologic evidence of tabes diabetica. Urinalyses: variable amounts of sugar. Occasional ketones. Fasting blood sugar varies from .295 to .500%. Blood urea nitrogen 19 mgms. Wassermann negative.

Summary Diagnosis: (1) Epilepsia tarda. (2) Diabetes Mellitus. (3) Arteriosclerosis. (4) Cardiac hypertrophy. *Course:* After the patient's regime of diet and insulin was properly regulated she had no more convulsions until 1926 when she broke diet. At present (4/7/27) she is quite well with urine free of sugar.

*Case No. XII.* (Endocrine Dysfunction type—Diabetes Mellitus with Hypertension and Arteriosclerosis). Mrs. D. M. Age 53. 10/3/23—Well until one year ago when pruritus vulvae and polyuria led to finding of sugar in urine. Had first convulsion nine months ago while cooking over hot stove. Second convulsion three weeks ago while ironing. Both preceded by vertigo and followed by heavy sleep for several hours. No tongue biting. No sphincteric incontinence. About ten days ago had a series of three brief convulsions without regaining consciousness between convulsions. No residual paralysis and no petit mal attacks but some loss of memory recently. Menopause six years ago. Two brothers died of diabetes. No epilepsy in family.

Examination: B. P. 195/120; Wt. 175; Height 65 inches; P. 72. Obese. Eye-grounds show marked indentation of veins by silver wire type of arteries. Heart shows occasional extrasystole. Left border is 3cm. to left of mid-clavicular line. Rough systolic murmur at aortic area. Urinalysis: Sugar 1.8%. No Ketones. Blood sugar, .245%. Blood urea nitrogen eighteen mgms. Wassermann negative.

Summary Diagnosis: (1) Epilepsia tarda. (2) Diabetes Mellitus. (3) Hypertension. (4) Cerebral Arteriosclerosis. (5) Cardiac Hypertrophy. *Course:* 4/15/27—Patient has been uncooperative as regards diet. Has had three convulsions in past two years. Following the last convulsion three months ago developed a right hemiplegia which has now almost disappeared.

*Summary* of the salient features of these twelve case-histories reveals some interesting facts. Five are men, seven are women. Nine are overweight. The average age at onset of convulsions is fifty-six years—with forty-one as the youngest and seventy-three as the oldest age of onset. Regarding the character of the seizures, all are of the recurrent, grand mal type. In two patients the attacks are exclusively nocturnal, in four exclusively diurnal.

Two patients exhibit, in addition to major fits, petit mal attacks. An aura, usually of precordial distress or vertigo, is noted by six patients. One case-history reveals an episode of status epilepticus. Tongue biting is mentioned in five cases, sphincteric incontinence in six. The only classical feature lacking in these convulsions is the initial cry.

The grouping of our cases is as follows: three arteriosclerotic, one hypertensive, three mixed hypertensive-arteriosclerotic (one of which is syphilitic), and five belong to the endocrine dysfunction group. Of the latter, three are cases of diabetes mellitus, one of hypothyroidism, and one of diabetes insipidus. Every case in this endocrine dysfunction group has either hypertension or arteriosclerosis or both in addition. In no case is there any evidence of marked impairment of renal function—except in case five which terminated in the uremia of prostatism five years after the initial convulsion.

The only underlying condition present in all cases is some circulatory abnormality. These abnormalities are divided as follows: (1) All twelve patients exhibit some cardiac disturbance, ten with definite hypertrophy and varying degrees of myocardial degeneration and two without demonstrable hypertrophy but with well marked systolic apical murmurs (in addition one of the latter shows sinus bradycardia in the electrocardiogram). (2) Ten of the twelve present definite evidence of arteriosclerosis as judged both by palpation and by ophthalmoscopic examination. (3) Seven are hypertensive. (4) Eleven patients present two or more of the above factors combined.

Only one patient (case 8) has neither demonstrable cardiac hypertrophy nor demonstrable arteriosclerosis, but she has hypertension and diabetes insipidus.

Prognostic points in our series are as follows: Two of the twelve patients have died—case 5 in coma five years after initial convulsion and case 9 of apoplexy one year after onset. Eight patients are alive—averaging at present almost four years of life since onset of convulsions. Two patients have not been heard from. Of the eight known living patients, two have had strokes and are confirmed invalids, two others have such marked myocardial and hypertensive disease as to be totally incapacitated, while four are able to lead fairly normal lives. The longest duration of life after the initial convulsion is that of case 4 (of the hypertensive group). This patient is alive and well (except for a blood pressure of over 200) now nine years since her first fit and three years since her last one. The second best showing is made by one of the diabetic group (case 11) for whom insulin came just in time and who is now well seven years after convulsions began.

With the facts of these case histories in mind let us return to a brief discussion of our belief that moments of deranged cerebral circulation are responsible in part at least for the convulsions of *epilepsia tarda*. Of course this thesis in regard to epilepsy in general is not original with us. Sir William Gowers (6) has emphasized it. Russell in his Goulstonian Lecture in 1909 (7) maintained that "the fundamental factor underlying both the ordinary faint and the epileptic fit is cerebral anemia."

Moon (8) presents a recent concise review of this hypothesis and reports a case of mitral stenosis with epilepsy at thirty-five. This report indicates the impossibility of sharply separating so-called idiopathic epilepsy from senile epilepsy.

It is well known that sudden disturbances of the cerebral circulation are sometimes followed by convulsions. They may occur, for example, during the rapid aspiration of pleural effusion, following profuse hemorrhage from any cause and they have been produced in man and animals by compression or ligation of the carotid arteries. In three patients with senile epilepsy Naunyn (9) was able, by manual compression of the carotids, to reproduce typical grand mal fits. He was also able to initiate fits in a few other non-epileptic but definitely arteriosclerotic individuals, whereas carotid compression failed to produce convulsions in a group of healthy adults. A recent significant and important study by Bordley and Baker (10) indicates that localized cerebral arteriosclerosis may be present without clinical evidence, and furthermore that such arteriosclerosis was found in all their cases of "essential hypertension." Just how the group of endocrine dysfunction cases of senile epilepsy might fall in line with our circulatory hypothesis is a little difficult to state. Of course all of our cases had, in addition to diabetes mellitus or insipidus or hypothyroidism, some definitely organic cardiac or vascular defect. We feel that the endocrine dysfunction factor is to be viewed chiefly as a cause predisposing to organic circulatory disease. The possibility, however, of sudden circulatory changes of

hormonal nature (comparable to the convulsions of insulin shock) cannot be excluded. We certainly do not agree with the prevailing French view (11) which would ascribe to acidosis the diabetic type of epilepsy. It is interesting to note in passing that the first allusion in American literature indicating a recognition of the diabetic type of senile epilepsy is that of Dr. Phillip S. Roy in a discussion of this subject in Washington, D. C., thirty years ago. (12).

Diagnosis of the several types of *epilepsia tarda* is by no means always easy. The physician who is called upon for an opinion either during or immediately following the initial convulsion certainly has many possibilities to consider. We may mention the more probable causes of generalized convulsions of adult life at this point: apoplexy, hysteria, general paresis, eclampsia, acute yellow atrophy, meningitis, encephalitis, brain tumor, Adams-Stokes disease, coronary artery occlusion, intoxication by alcohol, strychnin, belladonna, lead etc., sudden anemia from hemorrhage, cranial trauma, brain abscess, the various types of senile epilepsy, and finally uremia. It is the group which comprises the senile epilepsies, apoplexy, and uremia that offers the greatest difficulties to the diagnostician.

When more than one convulsion has occurred and an interval of comparatively normal health has intervened the diagnosis is easier. Such a history points strongly to one of the forms of *epilepsia tarda*, the diagnosis of uremia which is usually made is seldom correct. The difference in prognostic significance is very great—a patient

with true uremic convulsions is as a rule at death's door, a patient with *epilepsia tarda* may live for many years and may indeed be cured of his convulsions.

It is not sufficiently appreciated that generalized convulsions are rare in true uremia. It is significant, we think, that Strauss (13) noted no increase in the incoagulable nitrogen of the blood in cases of so-called uremia with convulsions. Agnew (14) states that "convulsions are probably not a part of pure nitrogen retention." In a more recent study of the syndrome of azotemia Feinblatt (15) found uremic convulsions surprisingly infrequent and when they did occur they were always terminal—in fact within an hour of death. We do not feel that the very rare condition of uremia without azotemia (16) is deserving of mention in this discussion. It would almost seem that azotemia inhibits epileptiform seizures. It follows that the diagnosis of uremia in an elderly subject with an initial convulsion should not be made hastily. One of the types of *epilepsia tarda* must be borne in mind.

In the treatment of *epilepsia tarda* the associated and underlying pathologic processes must be regulated as far as possible. As in idiopathic epilepsy so here the emphasis must be placed upon a quiet even mode of life with all sources of irritation—both physical and mental—eliminated as far as possible. A bland diet of the low salt, low protein type and small meals seems to us to be the most suitable. Constipation must be rigidly combatted. Bromides or luminals are usually indicated. Iodides may be tried. Thyroid extract seems to

have benefitted the convulsions in our case of hypothyroidism. Other endocrine substances are recommended but we have not been able to convince ourselves of their efficacy—always excepting insulin for the diabetic patients who need it. Digitalis and diuretics are sometimes indicated. In emergencies venesection has seemed helpful, as in one of our hypertensive cases.

The prognosis like the treatment varies with the underlying conditions. The cerebral arteriosclerotic "epileptic" may live for many years, although progressive mental deterioration is the rule. Sometimes paralyzes follow the convulsions. Anglade (17) reports several interesting cases of this type which came to autopsy. One of the patients had his first convulsion at sixty-three and lived to seventy-one. According to Etienne and Richard (18) the endocrine dysfunction type (non-diabetic) may be cured by proper therapy. Our own patient of this group was "cured" of her convulsions but died a year later of apoplexy. The hypertensive epileptic is always in danger of cerebral or cardiac catastrophe or terminal uremia. Anginoid attacks are not infrequent. One of our patients in this group is alive nine

years after her first convulsion. Theodore C. Janeway (19) states that in his series of 7,872 cases of hypertension "onset with convulsive seizure was a great rarity." In one case, however, "four years intervened between the initial uremic convulsion and death." This was doubtless a case of hypertensive epilepsy and not of uremia. The diabetic type of senile epilepsy is now perhaps the most hopeful of all—thanks to insulin.

#### SUMMARY

(1) Twelve cases of epilepsia tarda are reported and a classification is suggested.

(2) A background of combined circulatory defects is demonstrable in all cases—indicating the probability that moments of deranged cerebral circulation constitute one exciting cause of the convulsions in these cases.

(3) Differential diagnosis of the types of epilepsia tarda is presented with emphasis on their separation from uremia in which generalized convulsions are rare and only terminal.

(4) Prognosis and treatment are briefly presented.

(5) A selected bibliography is appended.

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# The Allergic Reaction, The Basis of Tuberculin Therapy\*

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## DIFFERENCE IN REACTION OF THE NON-TUBERCULOUS AND THE TU- BERCULOUS TO TUBERCLE BACILLI

**C**LINICAL tuberculosis is a disease which is usually engrafted upon an individual who has been previously infected by tubercle bacilli; and who, because of this fact, offers a special resistance to their growth and spread. If the secondary implantations are not produced by too large numbers of bacilli, the infection proves to be abortive or heals; or, if infection becomes well established, the resulting disease nearly always assumes a chronic course. That is, the tendency to proliferation on the part of the local cells exceeds the tendency to exudation and degeneration.

When bacilli first implant themselves in the tissues of a host the numbers that cause the infection are usually small. It is well that this is true; for, the only defense that is transmitted to the organism at birth is the natural defense of the tissues, enhanced by whatever degree of specific resistance may have been handed down from a race accustomed more or less to withstand tubercle bacilli. The specific al-

lergic quality of the cell is not yet present. This is acquired later as a result of the action of bacilli and bacillary products upon the tissue cells; consequently is not available until after the host has first sustained an infection. An infection is essential to the production of a competent and lasting allergy; although dead bacilli, and possibly bacillary protein, will produce a certain degree of allergy.

Tissues of the nontuberculous possess the power of reaction to foreign bodies as is shown by the formation of tubercle. This, however, is not a specific reaction but one called forth by all foreign bodies which gain access to the tissues. The reaction of tissues to the primary inoculation of tubercle bacilli is not unlike their reaction to bits of glass, stone and other foreign material. The resemblance of tubercle bacilli to foreign bodies in this particular is largely due to their waxy content which protects them from the destructive action of the tissues.

A given infection with tubercle bacilli, overcome or rendered chronic by the host, makes him more resistant to future infections by stimulating his cells to the elaboration of a defensive mechanism. A defensive mechanism is not raised to its highest point of efficiency at one time; but is cumulative,

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increasing as metastases, from already existing foci or from new infections from without are, successfully withstood. This defensive mechanism or immunity increases with each subsequent infection which the host is able to withstand, even though he may eventually be overcome by the disease. As clinical evidence of this immunity it is only necessary to cite the fact that while a few bacilli, becoming implanted, cause infection in one who has not been previously infected, millions and millions of bacilli may be discharged daily from ulcerations in the lung of one suffering from pulmonary tuberculosis and pass over the mucous membranes of the bronchi, throat and mouth without producing metastases. A guinea-pig receiving a second inoculation of small numbers of bacilli will live much longer than the pig inoculated only once. Experience at the Saranac laboratory shows that reinfected animals live at least twice as long as those receiving only one inoculation (1).

The chief factor which makes adult tuberculosis differ from that of childhood, and the essential factor in the successful combat of clinical tuberculosis, is this defensive mechanism developed on the part of the body cells as a result of the stimulation caused by tubercle bacilli present in infections prior to the implantation causing the clinical disease, and further stimulated by new implantations during its course.

#### THE NATURE OF THE SPECIFIC DEFENSIVE MECHANISM AGAINST TUBERCULOSIS

What this specific mechanism which protects the body against tuberculosis

is cannot be answered fully; yet the phenomena which have been observed in experimental animals and in the clinic give some idea of its nature. We know many things about it and have learned to recognize accompanying phenomena, even though we do not fully understand the process. While there seem to be many factors at work in protecting the organism against tuberculosis they result in two main effects: one, that of warding off reinfections or reducing their virulence; the other, that of healing existing foci.

Modern trends in immunology are following very closely the work of Metchnikoff (2) in dividing protective elements into *microphages* and *macrophages*; and the more extended studies of Aschoff (3) which have caused him to classify all cells of the body which possess the particular function of phagocytosis, likewise that of producing immunity and healing infections, as the *reticulo-endothelial system*, which he schematically outlines as given in Chart I.

The cells of the tuberculous animal possess the power to destroy the bacilli or, failing this, to surround them with an inflammatory reaction encapsulating them and preventing, or at least hindering, their spread. This is different from the non-inflammatory reaction which attends primary tubercle. This property of inflammatory reaction seems to be general in the cells throughout the body, and only awaits new implantation of bacilli to manifest itself. It is greatest, however, in tissues adjacent to tubercle and seems to vary somewhat in different tissues.

Koch (4) was the first to observe the difference in behavior of an animal

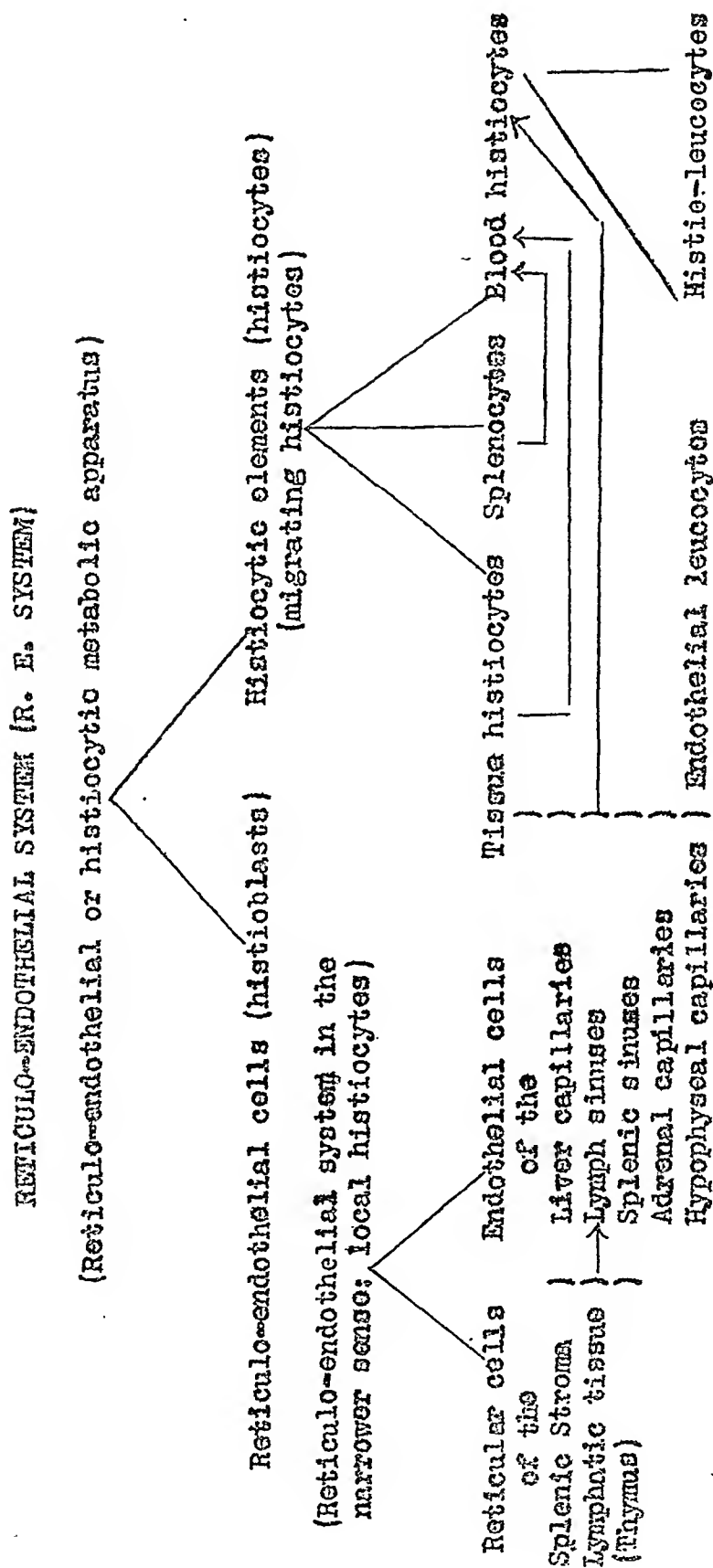


Chart I

toward a first infection and a reinfection. He noted that a first injection of bacilli into an experimental animal was followed quickly by a nodule which soon passed away, the bacilli being partly screened out in the regional lymph glands and partly passing on to the general circulation to cause infection in other organs. He observed further that after the animal was already infected a second injection behaved very differently. It produced a nodule at the site of inoculation, followed by an ulceration in a few days, which then healed, the regional lymph glands being only slightly or not at all infected. All of the elaborate studies of immunity in tuberculosis have centered about this observation.

Krause and Willis (5) and Krause (6) have studied the retarding effect of this immunizing mechanism on invading bacilli in reinfections and compared it with primary infection. They have shown that bacilli in the first inoculation of an animal will quickly pass into the general circulation while bacilli inoculated into animals which are already tuberculous pass beyond the defensive cellular barrier very slowly and only find their way into the general circulation after three or four weeks have elapsed. This is so important for the understanding of the defensive action of allergy that I will quote their findings:

"1. In normal nonimmune guinea pigs tubercle bacilli, inoculated intracutaneously or subcutaneously, are carried almost immediately (within an hour) from the portal of entry by the lymphatics.

"2. Within three or four days they have made the circuit of the body.

"3. In immune (allergic) animals their transmission is greatly retarded.

"4. They remain fixed at or near the portal of entry for about seven days.

"5. They do not reach the regional lymph nodes (superficial inguinal and axillary) until two weeks after infection.

"6. They do not become generalized to the body until three or four weeks after infection."

Many invading bacilli are engulfed by phagocytes as soon as they enter the tissues, some are destroyed and some again destroy the phagocytizing cells (2) (3). There also may be a lytic action possessed by the body fluids of immunized animals which destroys bacilli. Kraus and Hofer (7) noted that bacilli injected intraperitoneally into animals suffering from tuberculosis show degenerative forms in from fifteen to thirty minutes. It would seem that there are both fixed and circulating elements in the specific defensive mechanism against tuberculosis, but that the principal reaction is cellular and not humoral.

The non-tuberculous animal injected with large numbers of bacilli is not even made ill; but the tuberculous animal suffers a severe reaction and may even succumb in from 6 to 48 hours (Koch) (4). The same effects may be produced by tuberculin. Newly born (non-infected) children have received 500 and 100 mgm. of tuberculin without causing any more disturbance in their physiologic processes than would be caused by so much water (Schreibers) (Schlossman) (8). In the infected child, on the other hand, a few milligrams would cause severe reaction,

and very large doses might even produce death.

#### EFFECT OF DEAD BACILLI UPON THE IMMUNIZING MECHANISM

Koch (4) early observed that, when a subsequent infection took place in an animal already suffering from tuberculosis, the original foci showed signs of inflammation followed by healing. This was later confirmed by many observers. It led to the idea of attempting to cure tuberculosis by inoculations of living bacilli. To this end various types of bacilli have been tried. Many experimented with human bacilli of low virulence. Moeller experimented with certain acid-fast bacilli, particularly the timothy bacillus and the blind adder bacillus. Others used the avian and the turtle bacillus. While favorable experimental results were produced by living tubercle bacilli, the procedure was accompanied by too great danger to be used in the treatment of human beings.

Koch early experimented with bacilli which had been maintained at low temperature for a long period, also those killed by boiling and by chemicals and found that they produced effects similar to those caused by living bacilli. Sternberg confirmed this, finding that tubercle bacilli which had been killed by live steam, when injected intravenously into animals, produced the same pathologic changes that were caused by living bacilli. Caseous tubercles formed in which bacilli maintained their morphological characteristics for quite a long time.

Lowenstein (9) also confirmed the immunizing influence of dead bacilli and found a decided increase in resist-

ance to subsequent injections of living bacilli in animals which had received previous injections of dead bacilli.

Much experimentation on animals shows that small infections produced by living bacilli, could they be controlled, would undoubtedly be of value in the treatment of tuberculosis; but there are difficulties to be overcome which cannot be estimated and dangers that cannot be controlled. Likewise, the therapeutic employment of dead bacilli, while efficacious, is impracticable because of their local necrotizing effects. Nevertheless, some artificial means of maintaining immunity at a high level and of utilizing the specific allergic reaction in producing fibrosis and healing tubercle, if obtainable, is highly desirable.

#### TUBERCULIN STIMULATES SPECIFIC DEFENSIVE MECHANISM

Koch early turned the search from the dangerous living and the local necrosis-producing dead bacilli to the products generated by bacilli during growth and to emulsions made from their bodies. He developed the various tuberculins which bear his name, hoping that he might find some product made from bacilli which, without carrying with it the disadvantages of living or dead bacilli, would still evoke the specific allergic reaction of the tissues, maintain immunity at a high level, and promote healing. He worked on the theory that a remedy to be efficacious would have to increase the patient's immunity and produce the same inflammatory reaction about tuberculous foci as is caused by natural infections or infections experimentally produced in the bodies of human beings

or animals who are already tuberculous. If such a remedy could be attained, by controlling the dosage fibrosis could be hastened without danger of necrosis.

There are probably many factors which aid the organism in overcoming infection such as the lymph, blood and other cellular elements, particularly those belonging to the reticuloendothelial system; and the entire immunity response is favored by adequate nutrition and a well-balanced state of metabolism. It is perfectly evident that these specific allergic reactions, which are such important factors in the healing of tuberculosis, depend very much upon the maintenance of a state of physiologic equilibrium in the patient's body, as well as upon the specific bacillary stimulation itself; in fact, the immunizing response must be looked upon as an acquired physiologic reaction of the body cells. This fact is evident from the lowering or disappearance of allergy which is known to occur during periods of lowered vitality which accompany pregnancy, such infections as measles, scarlet fever and influenza, extensive active tuberculosis and other states of malnutrition and stress.

If we accept as fact that there is a specific protecting mechanism whose function is to heal tuberculosis, then we must inquire why it sometimes fails to protect the individual, and whether or not it is possible to increase its efficacy by artificial means. Frequently the infection is widespread, or it may be more limited but be very active. In either case there is great opportunity for new infections to take place caused by large numbers of bacilli, which may depress the patient's allergy and prevent a competent immun-

izing mechanism from being established; or the reaction may be so severe as to call out the exudative instead of the proliferative reaction. This is only another way of emphasizing the well recognized fact that tuberculosis should always be treated when the disease is limited in extent and inactive if best results are to be attained, and that advanced tuberculosis presents problems which are difficult to overcome.

We must never lose sight of the necessity of the local inflammatory tissue reaction in healing. This inflammatory reaction represents the acquired specific increased activity on the part of the body cells which is called out to aid the organism in combating the action of bacilli and their products. It limits the spread of bacilli and builds a fibrous wall about them, without which the body could not overcome infection. It is also evident that it must be more efficacious where the process is less severe and less extensive, because there is less opportunity for reinfection to occur, and such as do occur are apt to be caused by fewer bacilli and take place at longer intervals, hence cause the proliferative type of reaction, which consists of a slight hyperemia with little or no exudation.

This allergic reaction can be brought about in experimental animals by the injection of either living or dead bacilli; and when it has disappeared or is waning it can be restored by the injection of either living or dead bacilli or tuberculo-protein. Immunity can be heightened and a specific inflammatory reaction can be brought about in the tissues surrounding tubercle by the injection of preparations of bacillary protein which are of themselves unable

or barely able to produce histologic tubercle. This is the basis upon which the therapeutic effectiveness of those tuberculins rest which do not contain bacillary bodies.

It must be understood that two processes go on in tubercle simultaneously: one, caseation, in the center, destructive in character; and, the other, fibrosis at the periphery, conservative in character. Even though caseation is present in the center of tubercles, if the patient is able to put up a competent defense, those new infections which are produced by a few bacilli which repeatedly take place at the periphery are met by reaction which favors the production of fibrosis and the limiting or healing of tuberculous foci. Only reinfection by large numbers of bacilli is serious or dangerous. Every slight allergic reaction should increase the patient's immunizing mechanism and help to heal foci which are the subject of the reaction. Not necessarily every severe reaction, but oft-repeated severe allergic reaction has a tendency to produce necrosis in existing foci and favor dissemination of bacilli. The dose of tuberculin, however, unlike the natural spreading of tuberculosis in the host, is under control, and there is no reason why a reaction of dangerous proportions should ever be brought about if the physician understands the pathology of tuberculosis and the effect of tuberculin in causing the allergic reaction. Therein lies the value and the safety of the remedy.

With our recent comprehension of the allergic reaction and its part in the picture of tuberculous disease (Pottenger 10 and 11), as far as its character and course, likewise its healing, are

concerned, tuberculin should gradually come into its own and be recognized as a measure for taking advantage of the healing properties of the allergic response.

While tuberculin, in which I include all products containing bacillary protein, has not assumed the place in therapy that its specific action warrants, yet it must be recognized as having an action greatly desired in the treatment of the sluggish infiltrations and ulcerations of tuberculosis which though, at first, limited in extent do not heal because the necessary stimulating reinoculations fail to appear. The efficacy of this allergy stimulating action of tuberculin may be best studied in such visible local lesions as those of the eye, larynx, lymphatic glands, testicle, tongue and skin, although they are no more convincing than the favorable changes which appear in the carefully observed lung.

*Ocular Tuberculosis.* Tuberculosis of the eye is one of the most satisfactory of all tuberculosis lesion to treat. y. Hippel (12) reported in 1905 on 240 cases of ocular tuberculosis of all forms treated with tuberculin and showed healing in 75.7 per cent and improvement in 17.3 per cent more. While this was a far greater percentage of favorable results than ever had been produced by other methods of therapy, yet it was not sufficient to make tuberculin the remedy of choice in ocular tuberculosis because of the prejudice which was created against the remedy as a result of its wrong employment during its early period of trial; nor was it sufficient to stimulate those who treat tuberculosis of the eye to familiarize themselves with its use so

as to be able to use it effectively. My own experience in ocular tuberculosis has been limited to about a dozen cases, and my results have been nearly all satisfactory. I recently saw a patient whom I had treated successfully for tuberculosis of the iris eleven years ago. She had no recurrence in the meantime.

*Larynx and Tongue.* The larynx and tongue also present visible lesions which are convincing of the healing effects produced by tuberculin. I have observed hundreds of cases of tuberculosis of the larynx during tuberculin treatment and have noted the salutary effect of focal reaction in its influence upon the healing process. I have noted the same in tuberculosis of the tongue. The prognosis in tuberculosis of the tongue and larynx is favorable, unless dysphagia is present to such an extent as to interfere with nutrition, or, an accompanying pulmonary lesion is too extensive and too active.

*Adenitis and Tuberculosis of the Testicle.* Glandular tuberculosis and tuberculosis of the testicle are lesions that may also be watched during their treatment and are most convincing in their response.

*Pulmonary Tuberculosis.* My experience in the treatment of pulmonary tuberculosis now comprises several thousand patients, 75 per cent of whom were sanatorium cases and were closely observed. The treatment and after observation of these patients has extended over a period of thirty years. As a result of this experience I am convinced that the chances of cure in pulmonary tuberculosis can be improved greatly by the administration of tuberculin; that it not only increases the pa-

tient's chances of securing a healing but decreases his liability to a recurrence of the disease. This would be expected from its property of stimulating the allergic reaction to continue building up encapsulating fibrosis, after the stimulating natural reinfections have ceased to take place.

#### TUBERCULIN REACTION

As has been emphasized throughout this paper, an essential factor in the healing of tuberculosis is the focal reaction. Focal reactions produced by reinfection, inoculation of dead bacilli and tuberculo-protein are all the same. Slight reaction produces most of its effect in the periphery of the tubercle, increasing fibrosis and favoring encapsulation. Severe reaction, on the other hand, may involve the entire tuberculous focus and produce a severe exudation with necrosis. Natural reinfection in which only a few bacilli take part produces a fibroid form of tuberculosis with little exudation. This gives us the clue to the intelligent use of tuberculin. We must aim to secure the same effect as that produced by reinfection with few bacilli and avoid the type of reactions that are produced by reinfection with few bacilli and avoid the type of reactions that are produced by large numbers of bacilli (Pottenger 13).

That tuberculin is capable of doing harm as well as helping cannot be gainsaid. This is self-evident from the fact that it is capable of producing varying degrees of stimulation of the tuberculous focus, the same as accompany reinfections with varying doses of bacilli, but, if the clinician is conversant with the action of the remedy and understands the pathologic

process which he attempts to treat, danger may be avoided and only beneficial effects may be produced.

#### SUMMARY

1. The natural healing of tuberculosis is brought about by stimulating a specific immunizing mechanism, so that: (1) implantations of bacilli become difficult or are prevented entirely; and, (2) the inflammatory allergic reaction is brought into play in such a manner as to surround tuberculous foci with an encapsulating wall.

2. The specific immunizing mechanism may be called out by either living or dead bacilli, and when immunity is once established it may be increased by living or dead bacilli and bacillary protein (tuberculin).

3. The allergic reaction may be

taken as a measure of the specific defense in an infected organism.

4. The allergic inflammatory reaction about tubercle is necessary to healing, and can be artificially stimulated by tuberculin.

5. In the administration of tuberculin one can at will produce focal allergic reaction instead of depending on the haphazard stimulation of reinfections; and can carry them on after reinfections have ceased to take place, thus producing a more complete fibrosis and encapsulation of the bacilli; accordingly healing is hastened and the likelihood of relapse is diminished.

6. Slight reactions are necessary to healing. Occasional severe reactions may do no harm but are usually to be avoided.

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# Congenital Hypertrophy, Involving the Right Side of a Female Aged Six

By E. G. WAKEFIELD, B.S., M.D., *Brooklyn, N. Y.*

**D**URING the last decade the group of congenital anomalies which are characterized by an overgrowth of a single part, parts or the whole half of the body has received considerable space in medical literature. Too much has been said about the rarity, too many fanciful theories have been put forward to explain the etiology and too little has been said about a differential diagnosis for the most of us to have a clear conception of the anomaly and its accompanying conditions.

The statement has been made that this is the rarest anomaly known to medicine. This statement would be hard to prove or disprove but it is thought that the condition is not as rare as the literature would lead one to believe. The instances of the anomaly which are recorded are almost universally of extreme degree of a symmetrical development or are accompanied by a skin condition, a limp or something which has directed attention to the part. The literature shows that during the past thirty years, since Lablanc's report in 1897, the number of cases reported are two times as many as were reported during the sixty years preceding—an increase of about two hundred per cent. Of course the number of cases reported are too small to draw any conclusions however, the

increase is probably due to the fact that the anomaly is generally better recognized now than formally and the incidence is not greater. The following case report supports the belief that many of these patients pass unrecognized or if the anomaly is called to our attention it may be dismissed with some such diagnosis as lymphedema.

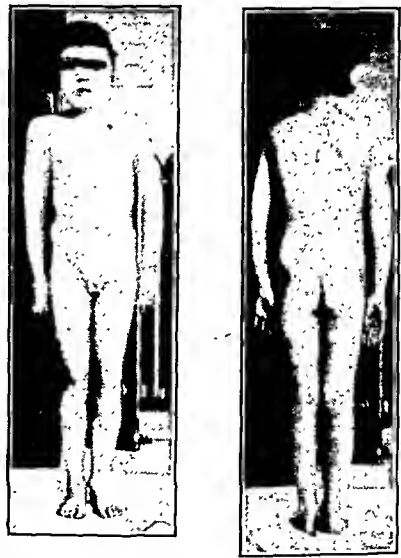


FIG. 1. CONGENITAL HYPERTROPHY

## CASE REPORT

The patient, an English girl aged six. She was born by a face presentation. Labor terminated spontaneously within about twelve hours. Immediately after birth she cried and seemed perfectly normal except for the swelling of the face which is inevitable. While the face was swollen the mother noticed that the right side was the larger and the right arm was the longer. The at-

tending physician assured the mother that the child was normal and that all the swelling would subside in a fortnight. The swelling of the right side of the face persisted and before the child was a year old she had been seen in several clinics in England. Everyone who saw the child expressed an opinion that the asymmetry would be outgrown in due time. The mother was repeatedly told that the child was afflicted with lymphedema. By the time the patient had reached her fourth year she had been seen in a few clinics in the United States and the mother received the usual assurance that the child would out grow the asymmetry. When the mother inquired about the disproportion in the size and length of the arms no one seemed to be willing to commit themselves.

The patient's father and mother have enjoyed perfect health. She is the eighth child of a family of nine children who are living and well. No other congenital anomalies had occurred in the family.

In the past she had enjoyed unusually good health. Chicken-pox is the only illness the mother could recall which had incapacitated the child in the least. The growth, except the right side, and development have been normal. By the end of the first year she could walk and speak a few words. During the past year the patient has attended kindergarten and received a prize for her good behavior and progress.

Except for the right side of the body a general physical examination showed a well developed and a well nourished child of about six years. The right side of the face and the right arm were developed out of proportion to the left. The right arm appeared the longer and the right side of the thorax appeared the larger. Height 122 cm., weight 23.6 Kg., the pulses, respirations and temperature were normal. No differences in temperature, sweating, texture of skin, growth of hair and nails or in the development of the teeth could be ascertained on the two sides. She was alert, polite, co-operative and well behaved. The pupils were equal in size, regular in outline and reacted promptly and correctly. On palpation of the tissues of the

right side of the face nothing unusual could be felt the only difference in the two sides was the size. No suggestion of edema could be elicited. The heart, lungs, abdomen, genitalia, peripheral and central nervous systems presented nothing unusual. Comparative measurements of the arms were as follows:

	Right	Left
Circumference of the arm at the insertion of the deltoid.....	17.5 cm.	15.0 cm.
Circumference of the arm 4 cm. above olecranon.....	18.0 cm.	15.7 cm.
Circumference of the arm 5 cm. below olecranon .....	16.5 cm.	15.5 cm.
Length from 5th dorsal vertebra to acromion process.....	14.0 cm.	12.0 cm.
Length from acromion process to elbow.....	28.5 cm.	26.0 cm.
Length from elbow to styloid of ulna .....	14.5 cm.	14.0 cm.
Total length of arm measured in tailor fashion from the 5th dorsal vertebra to wrist.....	56.5 cm.	52.0 cm.

Roentgen ray examination of the bones of the thorax, scapula, clavicles and bones of the arms and face showed nothing unusual. There were no demonstratable differences in the measurements of the bones from the roentgen ray plates; of course, such measurements are difficult and often inaccurate. The right leg measured a little larger than the left but the differences were so small that they were considered within the normal limits of variation. No asymmetry or deformities in the bones of the cranium could be made out. The Wasserman reaction was negative.

In making a diagnosis of congenital hypertrophy the first thing to be determined is there a hypertrophy of the large side or is there an atrophy of the small side. This may be very difficult at times. To illustrate, the late Dr. George Carpenter (2) showed a case of congenital hypertrophy to the Society for the Study of Diseases of Children in 1905 and he refused to commit himself as to whether the large side was hypertrophied or the small side was normal or atrophied when he was questioned.

Atrophy of the face, arm, leg or total hemiatrophy following anterior poliomyelitis, hemiplegia, nuclear lesions, muscular dystrophies or sympathetic paralysis can ordinarily be ruled out by the history and physical examination. If there still remains a question of nerve involvement electrical reactions of the nerves to the parts may be invaluable.

Congenital or acquired disease of the lymph drainage from the part or parts may be confusing. Persistent hereditary edema of the legs or Milroy's disease is an example of this type of affliction. In Milroy's (3) disease the edema varies from day to day and is strictly limited to the legs. Edgeworth (4) described a familial edema which is generalized, occurs in infancy and is ordinarily symmetrical. These patients die during the first few months of life. In countries where filariae abound and elephantiasis from filariae is common, this condition must be considered. Appropriate laboratory examinations will be of much aid even in chronic infestations. The history and a period of observation should be all that is necessary because filariasis is most common in adults and no asymmetry has existed since birth. Instances of the so-called "sporadic elephantiasis" which are non-parasitic in origin usually follow an injury or a surgical operation. Here the question arises, is the case reported above an example of sporadic elephantiasis? There is a history of injury of the face during birth. The points in favor of this being congenital hypertrophy not elephantiasis, lymphedema or some anomaly of the lymph drainage are; the asymmetry has maintained a normal relation dur-

ing the six years of growth, there has never been any periodical fluctuation in the size of enlarged parts, the skin is normal in texture and there is no evidence of thickening, there is no edema and the arm on the afflicted side is the larger and the longer. The arm did not receive any injury during birth. Edema, which is the result of congenital or acquired disease or abnormality of lymph drainage, begins in one place and spreads from there to adjacent parts and frequently there is a daily fluctuation in the amount of swelling and practically always thickening of the skin.

The rare condition known as facial hemiatrophy (5) which is characterized by a wasting of the soft tissues and bones of the face may be impossible to differentiate from facial hemihypertrophy if the process is not advanced to the stage that atrophy of the bones of the face can be shown in roentgen ray pictures. In this condition the asymmetry may be most striking as the atrophy stops exactly in the midline. Time is the most valuable differential factor if the history is not reliable, for in the late stages of hemiatrophy there are atrophic skin changes and falling of the hair. Other rare conditions which might be confusing are: scleroderma and sclerodactyle dystrophy (6). Both of these conditions are diseases of middle life and are accompanied by atrophic skin changes (7).

Congenital wryneck may be confusing in patients who have reached adult life. All that is necessary to remember about wryneck is that the tilting of the head in a fixed position during the period of growth will inevitably produce permanent deformity.

Some writers have included in the domain of congenital hypertrophy a certain group of hypertrophies which are congenital and are associated with tumor formation. Whether these asymmetrics should be classified as true congenital hypertrophy no one is prepared to say in the present state of our knowledge. To illustrate, Froelich (8) classified congenital hypertrophies as follows: simple hypertrophy, hypertrophy resembling generalized edema, and the increase in size which is congenital and due to tumor formation. Many writers have given different classifications. It is practically impossible to make a classification which is at all valuable. This fact is clearly illustrated by Campbell's (9) case which combined the features of Froelich's first and third classes namely hypertrophy and increase in size due to tumor formation. Instances of von Recklinghausen's disease might, if congenital, be difficult to exclude. However, instances of congenital von Recklinghausen's disease as reported by Harbitz (10) presented very little asymmetry.

Congenital hypertrophy is most commonly seen on the right side which is true of any anomaly. All sorts of skin lesions have been described as accom-

panying the hypertrophy. The skin disturbances are practically always vascular in origin. Mental deficiency, which was first fully considered by Greig (11) is present in from 15 to 20 per cent of the cases reported in which psychiatric examinations were made.

In a previous communication (12) some of the theories which have been advanced to explain the anomaly were enumerated. May it suffice here to say that none of the theories up to the present time will explain the partial, the total and the crossed hypertrophies. A working theory should explain all the various forms of a disease or it should exclude the forms which it does not attempt to explain. Practically all the exponents of the many theories on this anomaly, except one, (13) have been content to advance their theory and then silently repent. In the future when fashionable medical thought turns to something more obscure than embryology we are sure to have more interesting theories on this anomaly.

#### SUMMARY

1. An instance of congenital hypertrophy is reported.
2. A brief discussion of the diagnosis is given.
3. The anomaly is probably more common than the literature indicates.

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# The Saline Wheal Test as a Measure of The Blood Supply in Arterial Disturbances of the Extremities\*

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IT IS not my intention of entering into any polemic debate or theoretic discussion as to the nature of the diseases I intend to discuss or the physiology of the tests I am about to recommend as reliable guides to the sufficiency of the circulation.

The commonest symptom an orthopaedist has to deal with is pain in the toes, feet, ankles, calves and knees. After ruling out the evident cases of flat foot and other gross deformities, foot strain, bone, joint and nerve diseases, there remains, at least in our experience, a large number of cases whose only objective signs of trouble are more or less cold, clammy, cyanotic feet, blanching readily on assuming a horizontal or vertical attitude and quickly becoming cyanotic again on hanging down. This discoloration may take on many forms, it may be mottled, interspersed with patches of local anaemia, or with a sharp line (pseudo line of demarcation) about the toes just where the vamp of the shoe impinges.

In the old, such diseases commonly

are arterio-sclerosis, arterio-fibrosis, arterial spasm in Bright's disease and high tension cases, atheroma due to diabetes etc., general arterial calcification (often seen only or as a beginning in the vessels of the leg), aneurism and tumor.

In younger people there are the various forms of angio-trophosis (vasomotor neurosis) Raynauds disease, arteritis obliterans, erethromelalgia, etc., running all the way from chilblains to spontaneous gangrene. The nature and cause of these conditions are beside the question to be discussed this morning. Suffice it to say that in this day of little clothing and low shoes the milder types of trouble have become very numerous.

The pulse in the dorsalis pedis artery may or may not be absent. If absent then the case is fairly easily demonstrable as a serious interference with the blood supply of the limb; if the pulse is only altered in size it would be difficult to convince an unbiased observer of much circulatory change, while if the pulse apparently unaltered although the examiner might be absolutely convinced that he is dealing with a similar case he would be lacking all objective evidences of proof.

\*Presented before the American College of Physicians, at Mt. Sinai Hospital, Cleveland, Ohio, February 22, 1927.

Up to the present time but few good and practical methods of measuring the amount of the circulation have been devised. The most accurate of these is the calorimeter method in which a limb of known size and temperature is immersed for an arbitrary length of time in an adequate amount of water of known temperature. With suitable precautions against warming this water from the outside it can readily be deducted that the relative rate and amount of the increase in the temperature of this water must come from the blood circulation in the limb and thus a test for the sufficiency of the circulation.

One of the very best of the calorimeters is that of George Neil Stewart, Professor of experimental medicine at the W. R. U. this city, who assures us that the calorimeter method is so susceptible of error from outside influences and so delicate in its manipulation that it is only to be relied on when the test is performed in the physiological laboratory and is not in any way a test suitable for hospital or office use.

The hypodermic pyrometer method of Dr. Barney Brooks of St. Louis, depends upon the ingenious method of carrying the proper wires into a medium sized hypodermic syringe needle. After plunging this into the muscles of the limb to be tested and the normal temperature measured upon the galvanometer, a tight tourniquet is applied and the blood flow stopped. "The limb rapidly loses heat and when the bottom of the curve had been reached, the tourniquet is released and in a normal case this is followed by an immediate and rapid rise of temperature to its former level. In the tissues of an ex-

tremity in which there is impairment of the arterial blood supply the release of the tourniquet is not followed by an immediate and rapid rise of temperature. In any disease in which there is obstruction of the large arteries there is an appreciable period of from one to ten minutes elapsing between the removal of the tourniquet and the beginning of the rise in temperature of the tissues to be tested. In conditions of marked arterial obstruction the application and removal of a tourniquet may cause no temperature changes in the distal tissues. By the application of this method to the tissues of various levels and the distributions of main arteries it is possible to obtain valuable knowledge as to the condition of the arterial circulation of the extremity." We have not used this method because of the inherent inaccuracies of such small and delicate pyrometers and also because we do not feel justified in either making a small wound (not a harmless procedure in some of these cases by any means) or to apply a tourniquet (for so long a time.)

The direct injection of radiopaque substances into the arteries and to observe their progress by means of the fluoroscope does not appeal to my surgical judgment to be permissible in human beings suspected of having arterial diseases or obstructions, but it may well be that I am too conservative.

The oscillometer of Pachon seems to be a fairly reliable indicator of the pulsation of the artery at the level examined. Its weak points are that the instrument is forever out of order—and usually at the most critical times, cannot be used over or near bony points as

in foot, at knee or ankle, and depends for accuracy upon the patient's ability to lie perfectly quiet, which some old people with arterio-sclerotic gangrene seem to be unable to do. We have relegated it to be a check up upon the salt injection method and found but few discrepancies between them.

Following out the experiments of McClure and Aldrich who used intracutaneous salt solution injections for the purpose of studying edemas, Dr. M. B. Cohen of the medical staff of this hospital noted that while the appearance, size and shape of the wheal was more or less constant, the disappearance time varied in different individuals, and at times in different levels of the limb under observation. He conceived the idea that the disappearance time depended on the sufficiency of the arterial supply, and, since our orthopaedic department, as before said, was vitally interested in this condition and was checking up all the cases it could gather, we co-operated and examined jointly or independently over two hundred cases, and have drawn the conclusion that this method is entirely reliable and is the most convenient and simplest guide to the sufficiency of the arterial circulation of a limb. The physiology of this test is not for a mere orthopaedic surgeon to discuss.

The test is performed as follows: By means of a tuberculin syringe and a very fine needle, 0.2 cc. of 0.85 per cent salt solution is injected intracutaneously. The eye of the needle should be visible through the outer layer of the skin when the injection is made. The first injection is made at the base of the great toe, and similar ones are made at 4 inch intervals up

to the leg and thigh. The sense of touch is used to determine the disappearance time, as the vasomotor changes produced by the injection often render visual judgment unsatisfactory. Normally, sixty minutes or more is required for the complete disappearance of the wheal produced by the injected fluid, though readings as low as thirty minutes at the base of the great toe have been considered normal (as we have one such reading in a patient without clinical evidence of vascular disease); but as a general rule sixty minutes or more may be considered as the normal disappearance time. In cases in which the circulation is impaired the wheal disappears in less than this, in threatened gangrene, often as quick as one to five minutes.

We could cite many cases to support our contention and show the clinical value of this test. Only a few will be in order.

*Case I.*—A man, aged 38, stated that he had frozen his left foot while driving an open automobile in zero weather and was taken to a hospital, where the great toe was amputated at the metatarsophalangeal joint, about three months before he first came under our observation. There was an unhealthy looking ulcer over the head of the metatarsal bone. The pulse in the dorsalis pedis artery was missing. The foot was cyanotic and cold. A diagnosis of local arterial thrombosis due to frost-bite was made, and under appropriate treatment the ulcer was soon healed.

Two years later (December, 1925), he again "froze his foot" under similar conditions, and his little toe was amputated as an emergency measure. This stump also did not heal.

Three months later, the outer border of the foot, representing the area of skin sur-



rounding the metatarsal of the little toe, became black and gangrenous, and intense pain and suffering followed. Under the same diagnosis—local arterial thrombosis from frost bite—an amputation just below the calf of the leg was proposed and was to have been carried out. We were unexpectedly called for the second time at this point. No oscillometer was handy. With saline solution and a hypodermic syringe, we performed the intracutaneous saline test on both limbs.

The right leg showed a moderate circulatory deficiency, but the left (gangrenous) leg showed a disappearance time of the solution, as shown in table I.

TABLE I.—Disappearance time (Minutes) of Wheals on Left (Gangrenous) Leg.

1. Just above area of gangrene..	5
2. Ankle .....	15
3. Lower Calf .....	18
4. Calf .....	16
5. Upper Calf.....	20
6. Knee .....	30
7. Thigh .....	30
8. Upper thigh .....	60 plus

A diagnosis of generalized angiotrophosis with thrombosis of the left popliteal artery was made and a thigh amputation advised. A mid-thigh amputation was performed. The flaps and muscles hardly bled at all. An organized clot was found in the popliteal artery, and one or two of the calf muscles were found already gangrenous. There was only local arterial thrombosis in the foot; from the ankle to the popliteal space the arteries were patent. Later examination showed a blood viscosity of 6.10 (Hess).

The real explanation of this case is that the man (an inveterate smoker) was suffering from angiotrophosis (thrombo-angiitis form) and that the untoward exposure to cold brought on a rapid deterioration of the circulation.

Note: In December 1925 I was again called to see this patient. He now had a beginning gangrene of the right foot. Salt test showed almost no circulation—amputation had to be performed two weeks later to save the patient's life.

*Case II.*—A man, aged 51, stated that two years ago he lifted a weight of about 100 pounds, helping with the knee of the right leg, and while pushing upward felt something give way in the left foot, on which he was standing. He was soon unable to put any weight on the foot, which later became discolored and swollen and was treated by a competent physician for an acute strain of the plantar fascia. From that day on he could not work on account of severe pains in the left foot and ankle; the condition was much worse in winter; the feet at times turned blue. Roentgen-ray examination of both feet was absolutely negative; the man was a distinct hypopituitary type, with bilateral knock knees and flat foot. He weighed 206 pounds (93.4 Kg.) and was 5 feet 8 inches (173 cm.) tall.

Physical examination was entirely negative for signs and symptoms produced by injury. The feet were cold, rather livid, and blanched easily when the legs were elevated to an angle of 45 degrees, and the pulses of both dorsalis pedis arteries were barely palpable. The systolic blood pressure was 100; diastolic, 89, and the blood viscosity, 6.7 (Hess). The oscillometer showed a marked diminution in the swing over both ankles and calves; it also showed that the circulation in the right leg was just as insufficient as that in the left. The intracutaneous saline test showed the disappearance time diminished in both legs, as given in table 2.

In this case, through the combination of the viscosity and the intracutaneous tests, we were positively able to diagnose a case of thrombo-angiitis, which had been masquerading for several years under the diagnosis of a purely traumatic condition.

TABLE II.—Absorption Time (Minutes) in

Case 2.		
	Right	Left
1. Base of great toe....	14	13
2. Middorsum of foot..	16	15
3. Ankle .....	16	14
4. Lower Leg .....	25	32
5. Calf .....	36	37
6. Upper Leg .....	60 plus	60 plus
7. Thigh .....	60 plus	60 plus
Showing value of a negative test.		

*Case III.*—A man, aged 45, worked steadily until three months ago, when he dropped a heavy weight on the great right toe and fractured the first phalanx. This was treated by rest and splints. Since the accident, this foot had been cold and weak, and he could hardly walk on account of pain and weakness in the limbs. The intracutaneous saline tests taken in the course of the differential diagnosis showed a disappearance time of over sixty minutes in all parts of the thighs, leg, calf, ankle and foot, and a circulatory disturbance was ruled out. The cause for his condition proved to be a beginning lateral sclerosis.

*Case IV.*—In a man, aged 27, with bilateral thrombo-angiitis, the right foot was apparently much worse than the left. One toe of the right foot was ashy gray, but not gangrenous. The patient had had typical attacks of intermittent claudication, and the foot blanched on an elevation of 45 degrees. The intracutaneous saline test showed the circulation of the left side to be more deficient than the right, as will be seen from table 4. In order to check up the correctness of this test, the oscillometer was used by an intern who had no knowledge of these

findings; he found a marked loss in the swing of the needle on the left side and a better reading on the right, thus checking up this unexpected finding to a nicety.

TABLE III.—Absorption Time (Minutes) in Case 4.

	Right	Left
1. ....	22	10
2. ....	45	25
3. ....	48	29
4. ....	24	31
5. ....	36	35
6. ....	39	36
7. ....	36	38
8. ....	41	37
9. ....	48	42

#### SUMMARY

1. In the absence of edema, the intracutaneous salt solution test is a simple, rapid and accurate method of determining circulatory deficiencies in the extremities.

2. Sixty minutes or more is the normal disappearance time of the salt solution.

3. In all instances in which clinical circulatory deficiency exists, the disappearance time is diminished; in the area just above the seat of a gangrene (existing or threatened), it is frequently as low as five minutes.

# The Mitral Heart Roentgenologically\*

By DAVID STEEL, M.D., *Cleveland, Ohio*

IN ORDER to understand the changes in the cardiac silhouette under pathological conditions, it is, of course, quite necessary to know the normal. If you will bear with me for just a moment we will go over briefly the normal outline in the various positions.

On the right side in the A. P. position we notice usually two arches—the lower, larger arch being that of the right ventricle and the upper, less pronounced arch—that of the ascending portion of the aorta. In addition to these there can occasionally be distinguished two more. With a low diaphragm, and especially in the emphysematous, there is sometimes seen a small outward, concave shadow running downward in the cardio-diaphragmatic angle. This is the shadow of the inferior vena cava. The other shadow runs upward from the aortic shadow parallel to the spine save in its upper portion where it arches outward in the region of the clavicle. The parallel portion is regularly referred to the superior vena cava. It is less dense than the aortic shadow and can be differentiated fluoroscopically by a difference of pulsation. The upper arching portion of this shadow is cast by the right innominate vein.

The left side in the A. P. position

shows four arches which from above down are (1) aortic knob, (2) pulmonary artery, (3) appendage of the left auricle and (4) the left ventricle. In many cases the middle two are fused to form one—the so-called mid-cardiac shadow. Notice that below this the prominent left ventricular shadow forms an incisura—occasionally, and by far more common in children, we see a fifth left arch which occupies the left cardio-diaphragmatic angle. This arch is concaved outward and is ascribed by Groedel to adhesions of the pericardium to the diaphragm.

The right ventricle does not form a part of the silhouette in the A. P. position. It lies entirely anterior. A portion can sometimes be seen through a large gas bubble in the stomach.

Considerable knowledge is added by the oblique positions. In the first oblique position—i. e. the ray passing from the left posterior shoulder to the right anterior—quite a change takes place.

We now have an anterior and posterior border with a normal clear space behind the retro-cardiac or Holzknecht's space. Anteriorly (1) we see the aorta, (2) pulmonary artery (3) a small portion of the right ventricle (the amount depending on the rotation), (4) the left ventricle. Posteriorly we have from the above downward (1) a cross section of the pulmonary veins, (2) the left auricle, (3)

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the right auricle and (4) the inferior vena cava. Notice particularly the position of the left auricle and pulmonary artery.

In the second oblique view i.e. the ray passing from the right posterior to the left anterior—we see anteriorly (1) the ascending aorta—the best position for the study of the root. (2) a narrow portion of the right auricle and (3) the right ventricle. The greater the rotation the more is this arch formed by the right ventricle and the less the rotation the greater is it formed by the right auricle.

Posteriorly we see (1) the left auricle and the left ventricle. Notice in this view the positions of the right ventricle and the left auricle. In this position the rays run perpendicular to the aortic arch and we, therefore, have the classical position for the study of the arch and root. The descending aorta runs down along the spine shadow. This is also the classical position for the study of the left auricle, which sometimes can best be seen in the inverse second oblique.

The left auricle in mitral disease is the first to undergo dilatation. Due to congestion in the lesser circulation, and sometimes also to a sclerosis of the pulmonary artery, the right ventricle hypertrophies. It is the changes in this chamber that are responsible for a large proportion of our changes in the silhouette in mitral lesions. The right ventricle is situated anteriorly against the sternum and inferiorly against the diaphragm.

When enlargement takes place it can not go forward or downward and the result is a cardiac rotation. By this rotation the heart becomes more erect,

the left ventricle goes more posteriorly, the pulmonary artery comes more anteriorly and to the left, the left auricle is rotated further posteriorly and the aortic knob goes posteriorly and becomes partially hidden by the spine shadow. Stasis accounts for an enlarged pulmonary artery and left auricular appendage. These two structures will then fill out the cardiac incisura. The right auricle is not only made more prominent by pressure from the enlarged right ventricle but is enlarged because of stasis.

We have then in the A. P. position the following changes:—

- (1) Erect or oblique heart.
- (2) Prominent left auricular appendage.
- (3) Prominent pulmonary artery.
- (4) Insignificant or absent aortic knob. (Not only does rotation decrease the prominence of the aorta, but it is actually smaller due to habitual scanty filling.)
- (5) High junction of the pulmonary artery and aortic knob.
- (6) Elongated prominent right lower arch of the right auricle.

Additional information is added by a study in the oblique positions. Remembering that normally the left auricle is for the most part posterior, that it is rotated further posteriorly in mitral disease and that we have an enlargement, it is easy to explain the encroachment of the mid-portion of the retro-cardiac space in the first oblique view.

Normally this space is clear, but in mitral disease the auricle obliterates the mid-portion, leaving a clear space above and characteristically a clear, triangular area below. The enlargement in mark-

ed cases will displace the oesophagus to the right. In the second oblique view we not only make out a definitely enlarged left auricle but we can form some idea of the right heart as indicated by the increase of the arch. We can therefor add to the above:—

(7) Obliteration of the mid-portion of the retrocardiac space with a characteristic light triangle in the lower portion.

(8) Displacement of the oesophagus by the dilated and hypertrophied left auricle.

(9) An increase in the prominence of the right lower arch in the second oblique view.

In doubtful cases the hilus region is a definite aid.

We must grant first that the hilus region is formed mainly by the vessel shadows, the other structures forming only a minor part. Both hilus regions are increased in mitral lesions. The left side is obscured by the heart shadow, but the right side can usually be distinctly made out. In about one third of the cases the main branch of the pulmonary artery stands out sharply, being contrasted on its external side by the bright lung fields and on its internal side by the descending main branch of the right bronchus.

If measured at the level where the artery crosses the bronchus it will be found normally to vary between 11-14 mm. the average being 13. A measurement above 14 mm. therefor indicates some increased pressure in the lesser circulation, a fact which has some weight in questionable cases. We then have

(10) A change in the hilus region.

The above description is that of a

so-called mitral configuration. Often times when clinical findings suggest either a stenosis or insufficiency we find roentgenological evidence of both. The silhouette of pure stenosis shows no increase in the region of the left ventricle and the region of the left auricle is usually more marked. With an insufficiency we have a definite enlargement of the left ventricle as indicated by an increase of the left median distance. With enlargement of this chamber we have all four chambers involved and the result is a ball shaped heart. Also with an insufficiency the cardiac incisura is partially restored by the enlarged ventricle and the left auricular appendage does not appear as marked.

In summary we then have as signs of mitral disease:—

(1) Erect or oblique position of the heart.

(2) Prominent left auricular appendage.

(3) Prominent pulmonary artery.

(4) High junction of the pulmonary artery and aortic knob.

(5) Insignificant or absent aortic knob.

(6) Elongated lower right arch joining the ascending aorta higher up than normally.

(7) Obliteration of the mid-portion of the retro-cardiac space leaving a characteristic light triangle in the lower portion.

(8) Displacement of the oesophagus of the enlarged left auricle.

(9) An increase in the right lower arch in the 2nd oblique position.

(10) Changes in the hilus region.

(11) A ball-shaped heart in cases of mitral regurgitation.

## Studies in Rickets\*

By H. J. GERSTENBERGER, M.D., J. I. HARTMAN, M.D., JOHN D. NOURSE, M.D., NORMAN C. WETZEL, M.D., D. N. SMITH, B.S.,  
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INSTEAD of attempting to go into detail concerning the etiology, pathogenesis, pathology, symptomatology, prognosis, treatment and prophylaxis of rickets, I prefer to use this opportunity to acquaint you with some of the work which has been done at the Babies and Childrens Hospital by Drs. Nourse, Hartman, Wetzel and myself, in connection with human rickets.

Let me indicate too, that while progress has been made in the accumulation of knowledge concerning the etiology and treatment of rickets, but little has been accomplished in fathoming the pathogenesis of this disease. However, some progress also has been made in this direction. It is an accepted fact, for instance, that the inorganic phosphate content of the blood serum of rachitic infants is distinctly lowered, and that the glycolytic power of the blood is likewise reduced. In some phases of rickets the calcium level is but slightly below normal; whereas in others it is decidedly so. Whether the reduction of the glycolytic power of the rachitic blood is a result of the lowered inorganic phosphate content of the serum or whether both

characteristics are due to the same cause is not known. Nor is it even agreed that the changes found in the bones are secondary to the changes in the blood serum—some authors maintain that the characteristic changes in the blood serum develop only when rickets has reached a severe grade; some that all bone changes are dependent upon condition of the blood serum, and some that both abnormalities appear more or less at the same time, and are simply synchronous manifestations of the same disturbance.

Today, rickets is considered to be a metabolic disease affecting the body as a whole. Its clinical picture, however, is the result of pathological changes produced by it principally in the osseous system, the muscular system and the nervous system.

Its prime and basic cause is the inadequate exposure of the human body to the actinic rays. The type of diet, in our opinion, plays a secondary role; the proof of this latter statement are the following facts:

1. Exposure of the human body to the ultra-violet rays will cure rickets no matter what the diet may be.

2. Undiluted cows milk has been known by pediatricists to be rather an aid to the development of rickets than to its prevention.

3. Human milk, the ideal food for

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the human infant, can not be depended upon to protect the human offspring against rickets and will not cure this disease even though the mother ingest potent cod liver oil in the dose of one tablespoonful daily.

4. Human milk from a mother whose skin has been adequately exposed to the ultra-violet rays, cures active non-healing rickets in human infants.

In other words, the natural and primary combination for the human infant is actinic ray and skin, and not diet and gastro-intestinal tract.

During 1925 and 1926 we gave to three cases of active non-healing rickets, breast milk obtained from mothers or wet nurses to whom were given daily one tablespoonful of cod liver oil, beginning at least three weeks before the milk was ingested by the infants. In two cases the milk was canned, and in one case the milk was fresh, that is, it was taken directly from the breast. In all three cases no effect could be demonstrated either in the blood or in the X-ray.

We chose cod liver oil because we felt that it was a simpler method of administering the anti-rachitic factor to the mother than would be the exposure of her skin to the ultra-violet rays. However, in view of the fact that the cod liver oil ingestion was found to be of no value from the standpoint of curing rickets in the human infant, a finding which corresponded with results obtained by Alfred Hess in rats, we decided, especially in view of the fact that it was reported by Steenbock for goats and by Alfred Hess for human mothers that exposure of the integument to the actinic rays enabled the mother to produce a milk with definite

anti-rachitic powers, to expose human mothers to these rays and to feed their milk to active non-healing rachitic human infants. Hess fed the human milk to rats. The diets of the mothers receiving cod liver oil were just as complete as were those of mothers being exposed to the ultra-violet rays, and contained all of the essential food substances in sufficient quantities and calories.

In the two cases in which this method was used positive results were obtained. In other words, we were able to impart to human milk by exposing the skin of the mother to actinic rays, anti-rachitic properties of a degree sufficient to cure active human rickets. Just as in the cod liver oil series, one of the infants received this milk canned and the other in a fresh state.

These findings suggest the possibility that cod liver oil cures rickets in a different manner than does the actinic ray, and it again indicates that fundamentally human rickets is a disease due principally to an insufficient exposure to the ultra-violet rays rather than to the intake of an inadequate diet.

It has long been known, as was first emphasized by Wieland, that the most marked clinical signs of rickets are found in that part of the osseous system which happens to be growing most at the time when rickets is active, and McCallum, Howland and Kramer, and Cavins have shown that starvation of rachitic rats again starts calcification.

Recently, we published the results of observations made by us on the prevention of rickets in premature infants. It is well known that these human beings are especially prone to the de-

velopment of this disease. The sum and substance of our conclusions was:

1. That rickets can be prevented and cured in premature infants.

2. That the amount of cod liver oil required is small; the average daily dose for the group being 1.76 cc given in the form of S. M. A. or Protein S. M. A.

The diagnosis of rickets in our work was and is based principally upon the results of the calcium and inorganic phosphate determinations of the blood serum, and also on the roentgenological pictures of the wrist. Clinical examination in early cases of rickets in our experience is less dependable. No definite clinical signs were found in any of our cases.

In the study of the material which formed the basis of this report, it seemed to us that the prevention of rickets was easier when the gain in weight was relatively slow, and more difficult when it was excessively great and rapid.

In the series just referred to, two of the seven infants receiving Protein S. M. A. developed rickets. Both of these infants, however, lost their rickets even though they were continued on the same mixture and were not given more of the anti-rachitic factor in any form. These two infants gained remarkably in weight, but as they grew older, their relative gain in weight became less and the actual quantity of cod liver oil ingested, slightly greater, because of a slight increase in the food consumed. The increase in the cod liver oil intake however, was very slight, being not more than the 0.1 to 0.2 cc of cod liver oil per twenty-four hours. Consequently, it was our impression that

the principal factor for the healing of the rickets in these two infants, was the relatively reduced rate of growth, and that the opposite condition, namely, the earlier excessive high rate of growth, brought about the development of rickets. One of these infants weighed 1050 grams at birth, and was one of twins. The other twin weighed 1150 grams at birth, and gained at a slightly less rapid rate, and avoided the development of a definite rickets. In all probability in this second twin rickets was on the road to be developed in a recognizable form, inasmuch as there was a drop in the calcium and inorganic phosphate figures to levels which are considered to be just within the boundaries of normal. After this very temporary drop, the amounts of calcium and of inorganic phosphate in the blood serum rose to levels that are unquestionably normal.

In searching for a basis of study to determine the role of the rate of growth in increasing the requirement of cod liver oil in the prevention of rickets in essential normal premature infants we decided to use the daily gram gain in weight per kilogram body weight.

Our impressions were corroborated by one of our group (Dr. Wetzel) who found that the infants of our series who temporarily developed rickets, received for varying periods less cod liver oil per gram gain in weight per kilogram body weight than did those who did not. For instance, the one twin who developed rickets, gained during the preceding period, from 19 to 13 grams per day per kilogram body weight, whereas the brother who did not develop definite rickets, gained



from 11.5 to 9.0 grams. Inasmuch as the intake of cod liver oil for these twins was virtually the same during the period previous to the development of rickets, the only varying factor of any importance upon which we could put our finger, was the much greater gain in weight per kilogram body weight in the sister over the brother. Evidently, age and heredity could play no important part in these twins.

On the basis of these findings, a curve was constructed, indicating the amount of cod liver oil per daily gram gain in weight per kilogram body weight, presumably necessary to prevent rickets. The relative positions of the various infants of our first series to this curve were registered, and it was evident that the infant developing definite rickets was below this curve for a much longer period than was her twin brother who had a very temporary drop in his calcium and inorganic phosphate serum figures without developing dependable signs of rickets.

We have since then used this curve as the determinant of the amount of cod liver oil to be used in the prevention of rickets, in a series of seven premature and one full-term infants. These infants were observed for periods of four to five months, which is ample time for the development of rickets in growing premature infants not exposed to the action of the anti-rachitic factor. X-rays of the left wrist were taken at weekly intervals; estimations of the blood serum calcium and inorganic phosphate were made 1-2 weeks after admission in four cases; 3 weeks in three cases, and 7 weeks in one case, and thereafter in every instance at periods of two to four weeks.

The infants were examined at frequent intervals for clinical signs of rickets.

The maximum daily average amount of cod liver oil was 0.71 cc, and the minimal 0.4 cc; for very short periods the maximal amount of 0.2 cc and the minimal amount of 0.1 cc were given in some cases. The total amounts of cod liver oil received during the periods of observation from 117 to 154 days varied for the individual infant between 55 and 95 cc. An infant receiving the customary dose, namely 1 teaspoonful three times a day, during this same period, would have received a total of 1800 to 2200 cc, or in other words, twenty to thirty times more than we have found effective. Only one infant developed definite evidence of a mild rickets (X-ray and Blood) which properly healed on the same diet without any increase in the actual amount of cod liver oil received. The rate of growth, however, was less during this healing period and consequently the relative amount of cod liver oil per gram gain in weight per kilogram body weight was consequently greater. This infant gained in weight at a greater speed than did any other, except one, whose cod liver oil intake, however, was 30% greater. We believe this to indicate that the amount of cod liver oil used by us in this series as determined by the curve employed, is very close to the minimum amount required to prevent rickets. The possibility of such an occurrence was anticipated by Dr. Wetzel who constructed a second curve, which allows a 10% increase as a matter of safety. We at first thought that we should use the second curve as a surer method of preventing rickets. How-

ever, we chose the first curve in the anticipation of obtaining an experience such as we have just reported, which we feel is more valuable than an absolutely negative finding in every case.

From experience obtained in this second series, we have concluded as follows:

1. That rickets can be prevented in rapidly growing premature infants by the early and continued use of cod liver oil.

2. The amounts of cod liver oil required per day to prevent rickets in well infants, is small and varies directly with the rate of per gram gain in weight per gram per kilogram body weight.

Consequently, the actual amount of cod liver oil required per twenty-four hours is greater, the younger the infant. This seems paradoxical, but we are convinced that it is correct.

The cod liver oil requirement as determined by the curve used by us, gives quantities that are very close to the needed amount of cod liver oil used by us to prevent rickets. As the cod liver oil administered by us was in some

form of the S. M. A., we do not suggest that straight cod liver oil in such small amounts as 0.4 to 0.7 cc per day be used in practice. Nevertheless, we believe that straight cod liver oil, if given continuously, after the first week of life, will prevent rickets in normal infants, even though the amounts be much smaller than the customary dosage. The giving of cod liver oil within one week after birth should become a routine, throughout the entire year, inasmuch as newly born infants are usually protected against the sun. We are at present attempting by the same method of study as outlined above to determine the minimal amounts of straight cod liver oil required to prevent rickets.

From two illustrative cases it will be seen:

1. That the amount of cod liver oil became less as the infant grew older.

2. That the one infant remained free from rickets throughout the period of observation.

3. That the one developing rickets lost it without any change in diet.

# Mixed Tumor of Parotid Type, Orbital in Location

By EARL D. CUMMING, M.D., *Cleveland, Ohio*

ON OCTOBER 17, 1921, Mrs. Minnie Beese, age 52, presented herself at St. Luke's Out Patient Department for physical examination, with two complaints:

(1.) Pain in lower right abdomen, and

(2.) A prominence, very pronounced, of the right eye.

*Present Illness:* For the past seven years patient has had intermittent attacks of pain in the right lower abdomen associated with tenderness on pressure at approximately McBurney's point. She has never had nausea or vomiting with these attacks, and it is this disturbance that lead her to consult a physician rather than the prominence of her right eye, which she accepted as a matter of course. About three years previously she had had profuse lacrimation from the right eye and consulted an oculist, from which time she had noticed that that eye was becoming more and more prominent. When she closed the left eye and looked only with her right eye, she became nauseated. She noticed that her vision in the right eye was becoming less and less acute.

*Past History:* Patient was operated

upon 19 years ago for ectopic pregnancy. She had had an osteomyelitis of the right forearm and left femur when eight years of age. She had had nocturia for the past seven weeks. No abnormal amounts of urine. Menopause two years previously. She had three children; two living, one died of diphtheria, one miscarriage, and one ectopic pregnancy.

*Family History:* Negative.

*Physical Examination:* Patient was an obese woman weighing 198 lbs., and measuring 5 feet, 2 inches, in height. There was a definite right-sided unilateral exophthalmos, but the palpebral fissure on the right side was narrower than that on the left—intra-ocular pressure was normal on both sides. With the eyes rotated caudad there could be palpated under the supra-orbital ridge an irregular mass,  $2\frac{1}{2}$  cms. long and about  $1\frac{1}{4}$  cms. wide—slightly movable and painless. She was referred to the eye department, where her vision was 61/10-3 in both eyes. Her retinæ were essentially negative. Both pupils were equal and active. The patient's blood pressure was 182/104. Her left cardiac border was 2 cm. to the left of the mid clavicular line. The upper cardiac border at the third rib, and the right border of the heart corresponded with the right border of the

\*Presented to the American College of Physicians, St. Luke's Hospital, Cleveland, Ohio, February 22, 1927.

sternum. The aorta was slightly widened. Palpation corroborated the evidence gained by percussion as to the left border. Auscultation revealed both sounds of normal quality and intensity over the various valvular areas. There were no murmurs.

An examination of the lungs revealed a few coarse rales at both bases posteriorly. She was afebrile. Her pulse was 80. The abdomen was very thick walled and pendulous. It was very difficult to palpate the spleen and liver, neither of which were enlarged to percussion. There was some tenderness on deep pressure at McBurney's point. Vaginal examination revealed no abnormalities. Neuro-muscular examination showed all tendon reflexes, with exception of the achilles on both sides, present and active. The plantar response was normal bilaterally.

The urine showed an occasional hyaline and coarsely granular cast, and a few W. B. C's.

R. B. C.	W. B. C.	Hb.
5,840,000	5,840	90% Tallquist
Ewald Meal: Combined acidity.....27%		
Free acidity.....35%		
Total acidity.....62%		
No occult blood....Very few		

W. B. C., numerous squamous epithelial cells present.

The spinal fluid was under normal pressure, showed 6 cells, negative Globulin and Wassermann. The blood Wassermann was negative.

The pre-operative diagnoses were:

1. Orbital Tumor, right side.
2. Obesity.
3. Chronic Myocarditis.
4. Chronic Nephritis.
5. Hypertension.
6. Chronic Appendicitis.

On the 8th of November, 1921, Dr. Simonds and Dr. Shackleton removed the orbital tumor, which was fatty in appearance, lobulated, and measured  $2\frac{1}{2}$  cms. by 2 cms. by 1 cm. The microscopic section by Dr. King, corroborated by Dr. Mallory was Mixed Tumor of Parotid Gland Type. Following the operation Dr. May inserted 50 mg. of radium into the incision, screened by  $\frac{1}{2}$  mm. of silver, 2 mm. lead, 3 mm. of rubber and this was permitted to remain for nine hours. She made an uneventful recovery except for a ptosis of her right under lid, and a retraction of her right eye ball. Up to the present moment the patient has had no recurrence of her tumor and her vision is OD 20/60. OS 20/20. Her blood pressure, urinary findings, and cardiac findings have remained essentially the same, but her weight has dropped to 171 lbs., and she feels perfectly well.

*Conclusions:* My only excuse for reporting this case is the unusual location of this type of tumor. In the literature I have been able to find only four cases of mixed tumor of the parotid type found in the orbit.

In the December 1926 number of the American Journal of Medical Sciences, Joseph McFarland of Philadelphia reports ninety tumors of this type which came under his observation, and collected from the literature 269 other cases, and gives a comprehensive and complete resume of the histological and embryological study of the subject. In none of McFarland's cases was the tumor found in the orbit, but usually they occurred in or around the parotid, or other salivary glands. The theory of accidental sequestration of embryonal cells during the early and compli-

cated development of the face and neck affords the most satisfactory explanation of the origin of these mixed tumors. By that theory it is easy to account for the variety of tissues found in the tumors and for their varying proportions and conditions. They are individual entities, and have no relation to the normal structures in which they occur, and from which they do not arise. He thinks that they should be called "Mixed Tumors" and nothing else. They are inherently benign, but commonly recur after excision, and if frequently disturbed become destruc-

tive and invasive without giving metastasis. The histology is extremely complex—but on that account the microscopic diagnosis is usually easy. Histologically, prognosis is very difficult to determine, and is often misleading. Malignant change whether "sarcomatous" or "carcinomatous" in mixed tumors must be rare, and its occurrence is difficult to prove. Intervals of ten, twenty, or even thirty years may elapse between operative removal of a mixed tumor and its recurrence, therefore, caution should be exercised in declaring any case to be cured.

# Chronic Ulcerative Colitis

By HORACE W. SOPER, *St. Louis, Missouri*

UNDER the term colitis we consider the ordinary catarrhal form as well as the chronic ulcerative type. Chronic ulcerative colitis must be differentiated from tuberculosis, syphilis, post dysenteric ulcers and polyposa intestinalis adenomatosa.

Chronic ulcerative colitis has been a medical problem for many years. It has been designated idiopathic, non-specific, post-bacillary, infectious and septic ulcerative colitis. It appears to have been described as a disease entity by Wilke and Moxon (1) in 1875 and White (2) in 1888. There has been a great deal of difference of opinion as to the etiology of the disease. Logan and his co-workers considered some metabolic disturbance as the etiologic factor. Hurst (3), Einhorn (4), Leusden (5), Thorlakson (6) and most of the German writers considered the dysentery bacilli as being the original invaders. Prof. L. Kuttner (7) and Rosenheim (8) have both reviewed the subject recently and suggested the name of chronic suppurative colitis. They believe it follows bacillary dysentery. Streptococci are thought to be the etiologic factor by Jex-Blake (9), White, Yeomans (10), Wallis (11), Hewes (12), Lockhart, Mummery (13), Rolleston (14), and T. R. Brown (15).

Logan (16) from the Mayo Clinic in 1919 gave the most comprehensive description of the disease and presented x-ray plates and pathological specimens. He concluded "that chronic ul-

cerative colitis is a disease of long duration. The final stage ending quickly from toxemia or perforation. Nature's efforts to cure causes excessive fibrosis with resultant deformity of the colon. The forms of treatment are thus far unsatisfactory. The best results come from dieting and giving surgical rest to the colon."

In December 1925 Bargaen and Logan (17) published their article on, "The Etiology of Chronic Ulcerative Colitis." They found a diplococcus which they believe to be the primary etiologic factor. They made cultures from the lesions of sixty-eight patients suffering from the disease and found the organism in 80% of the cases. Twenty healthy colons were swabbed in the same manner and only once were diplococci of similar characteristics isolated. Their chain of evidence appears to be complete. They injected rabbits with the brain broth culture and produced a diarrhea and lesions of ulcerative colitis. Rabbits were injected with various strains of streptococci and the lesions in the colon were not produced. In persons suffering from ulcerative colitis they isolated the diplococci in periapical abscesses and in the tonsils. The culture was injected in rabbits and dogs, producing ulcerative colitis. The organism is a Gram-positive, lancet shaped diplococcus growing in twos and fours and has been observed with a capsule occasionally. Therefore it resembles a pneumococcus. They prepared a vaccine fil-

trate and used it extensively in the treatment of these cases and have obtained very good results. When the lesions were low enough for irrigation they treated with silver nitrate, lunar caustic, mercurochrome and hot water. They also consider that an important adjunct to the treatment is the tincture of iodine by mouth.

The findings of this organism in distant foci and the production of acute lesions in the colon could account for the repeated exacerbations of the disease.

Buie (18) gave a very good description of the proctoscopic picture. "In the early stages the membrane is granular, bleeds easily, is diffusely edematous and hyperemic. This is followed by various gradations of ulceration. The small white spots noted in the hemorrhagic membrane were in fact small miliary abscesses which finally form superficial ulcers. Later on the membrane has a granular glazed appearance with only tufts of mucosa here and there. Small polypoid growths of mucous membrane are occasionally scattered throughout the region of ulceration. When healing occurs small pit-like scars are formed."

The culture of the diplococcus is really a very difficult matter. It grows readily in the brain broth culture but the isolation from other organisms requires a great deal of bacteriologic skill and patience.

The diagnosis of chronic ulcerative colitis cannot be made without the use of the proctoscope and the x-ray barium enema. In our experience a large number of the cases are limited to the rectum and pelvic colon and do not involve the rest of the colon before a later period. However, some of the

X-ray plates show that isolated segments of the colon may be rarely involved.

I am sure that we have seen a large number of early cases involving the rectum and pelvic colon that have been completely arrested by means of local treatments. These local treatments have included mercurochrome in one per cent solution and the use of various powders applied by means of a special insufflation apparatus. Equal parts of calomel and bismuth subcarbonate is our favorite powder. After healing, characteristic pit like scars remain visible in various areas of the mucosa. In many areas the veins reappear and the membrane appears to be perfectly normal.

All the older proctologists describe a hemorrhagic proctosigmoiditis which is limited to the rectum and pelvic colon. It occurs in distinct attacks and is amenable to local treatment. I have verified this observation in a large number of cases and believe that the disease is a definite clinical entity. I have never seen a case that involved the whole colon. It usually clears up within two or three weeks' time under local treatment. It may be possible that it is a self limited disease and would disappear without any form of treatment.

Ileostomy has given a great deal of service in some of our cases but I would not advise the operation except as a last resort. Our best results have been secured by bed rest, high vitamin diet, as advocated by Dr. Larimore, and the use of mercurochrome in the rectum as well as the keratin coated tablets by mouth. I believe the best form of treatment to consist of keratin coated tablets of mercurochrome by mouth combined with local treatments of the lesions that are visible with the

sigmoidoscope. In some of the cases we have passed a small soft rubber catheter through the sigmoidoscopic tube and applied the powder by means of the insufflation apparatus. I would not advise dilatation of the colon in the late cases because of the friability of the gut. Blood transfusions are of great value in all cases of long duration.

Chronic catarrhal colitis may show a disappearance of the haustration in part of the colon particularly in the descending and pelvic colon, but it does not present the rigid gas-pipe like appearance of ulcerative colitis.

Patients with amoebic dysentery of long standing present an irritable colon with dilations and contractures here and there without loss of haustration. Luetic lesions are usually limited to the rectum and the lower half of the colon and are most likely to form local stricture formations. Tuberculous ulceration of the colon does not result in the loss of haustration but forms isolated contractures and defects.

This study is based on thirty-two cases of chronic ulcerative colitis. The Bargaen diplococcus was isolated in sixteen of them. The remaining sixteen cases were studied before the appearance of Bargaen and Logan's paper. The vaccine filtrate was used in ten of the cases with somewhat disappointing results. I shall proceed with abstracts of several case histories illustrating our results in treatment.

*Case I.*—Female, age 36. Came under observation in June 1922. She gave a history of chronic diarrhea of five years' duration. She consulted Dr. Bertnam Sippy three years ago and received various treatments including irrigation but continued to get worse. Finally in May 1921 the operation of ileostomy was performed under Dr. Sippy's direction. She was better for a time but the

diarrhea persisted and she gradually became addicted to opium. She used the tincture, taking from ten to sixty drops daily. Has been an invalid since the operation, confined to bed a greater part of the time. The sigmoidoscope, one-half inch tube, could be introduced into the greatly contracted rectum. The mucosa was covered with blood and pus, thick, velvety and bleeds easily. Barium enema revealed the presence of high grade exudative colitis. Entire colon was dehausted, tubular and rigid. She has been kept under careful observation ever since. She was treated by irrigations of the colon through the ileostomy opening as well as by rectum. One per cent solution of mercurochrome gave her less pain than any other agent used. She continued to be a semi-invalid. Colon continued to contract until in the Spring of 1925 it was markedly smaller in caliber, the rectum contracted down so that it would receive only a three-eighths-inch tube. The mucosa of the rectum by this time had apparently entirely disappeared leaving only bloody scar tissue. X-ray taken at this time showed the cecum to be considerably dilated. She had a great deal of abdominal pain and had to use opium in larger doses. It was frequently found that the blood and pus discharge from the cecum would soil the ileostomy opening. Because of this fact, her continued invalidism and constant pain requiring the use of opium, colectomy was decided upon. The operation was performed by Dr. Vernon Mastin and because of the tremendous amount of fat in the mesentery, presented considerable technical difficulty. About six inches of the rectum was left. She made a very satisfactory recovery and has improved very much since that time. She is free from pain, never requires any sedative and expresses herself as being very comfortable, up and about, very active and cheerful. The ileostomy is easily managed and occasions no discomfort. Her diet consists of all well cooked foods plus fruit juices. Feces analysis shows soft, mushy stools, free from mucus, pus and blood with good digestion of the fats, starches and muscle fibers. It has a faint acid odor but is free from the odor characteristic of colonic feces.

Recent roentgenograms reveal that food remains in her alimentary tract fourteen



hours. The entire small intestine is better visualized than is usual. The barium remains in contact with the various segments a considerably longer time.

#### DESCRIPTION OF THE RESECTED COLON BY DR. GEO. IVES

The specimen in formaldehyd solution is a colon with small portion of ileum attached. It is 79 cm. in length from the tip of the cecum to the severed end.

The greatest diameter of the specimen is 4 mm. at the cecum, the smallest diameter 15 mm. at the severed end. The thickness of about 9 mm. The most prominent part of the specimen is a fatty submucosa which measures from 2 to 8 mm. in thickness with an average thickness of about 6 mm.

The colon is imbedded in a considerable amount of fat, the epiploica are large and pendulous, the fat shows a considerable amount of congestion and many small hemorrhages, possibly occasioned by the operative removal. The whole specimen has the appearance of being contracted. The wall is greatly thickened, the increased thickness being caused, for the most part or entirely, by a layer of fatty tissue between the circular muscle coat and the muscularis musosae. The thickness of the layer of fatty tissue varies from 2 mm. to 8 mm. and is continous throughout the specimen, both in the colon and in the ileum. To a slight extent the fatty layer continues into the appendix.

The mucosa is covered, except for a short distance at the severed end, by a thick friable fibrinohemorrhagic exudate, which is greatly cracked and fissured, and there can be found grossly, no evidence of a normal mucous lining. Small dried granular pieces 5 to 6 mm. in diameter have been detached from

the inner surface in various places. These have the appearance of being dried blood clots. The muscle coats may be easily separated as may also the individual muscle bundles of the circular coat.

#### MICROSCOPIC EXAMINATION

The most prominent feature of each section is the fatty layer in the submucosa, which measures from 2 mm. to 8 mm. in thickness. This layer shows simply fatty tissue without any inflammatory reaction.

The surface of the mucosa throughout the specimen is covered with an acute hemorrhagic exudate. The mucous membrane is ulcerated in many places and where found is atrophic. The greatest amount of ulceration is in the transverse and descending colon. Beneath the mucons surface is a chronic inflammatory reaction consisting most of plasma cells. These cells extend down to the muscularis mucosae and make up most of the tissue of the mucosa, though a few polymorphionuclear leucocytes have infiltrated the tissue. This neutrophil reaction is most marked in the descending colon and is entirely absent in the ileum and cecum. Throughout the mucosa are found epitheloid cells, many of them showing mitotic figures.

The gross and microscopic picture is that of an acute ulcerative colitis superimposed on a chronic inflammation of the mucous membrane, plus the marked fatty infiltration of the submucosa.

This report of Dr. Ives differs from other descriptions that I have seen in the literature. I believe no one else has called attention to the tremendous amount of fatty tissue in the submucosa. There does not appear to be any fibrosis or connective tissue increase.



FIG. 1. Case I. This film was taken when patient first came under treatment (June 1922).

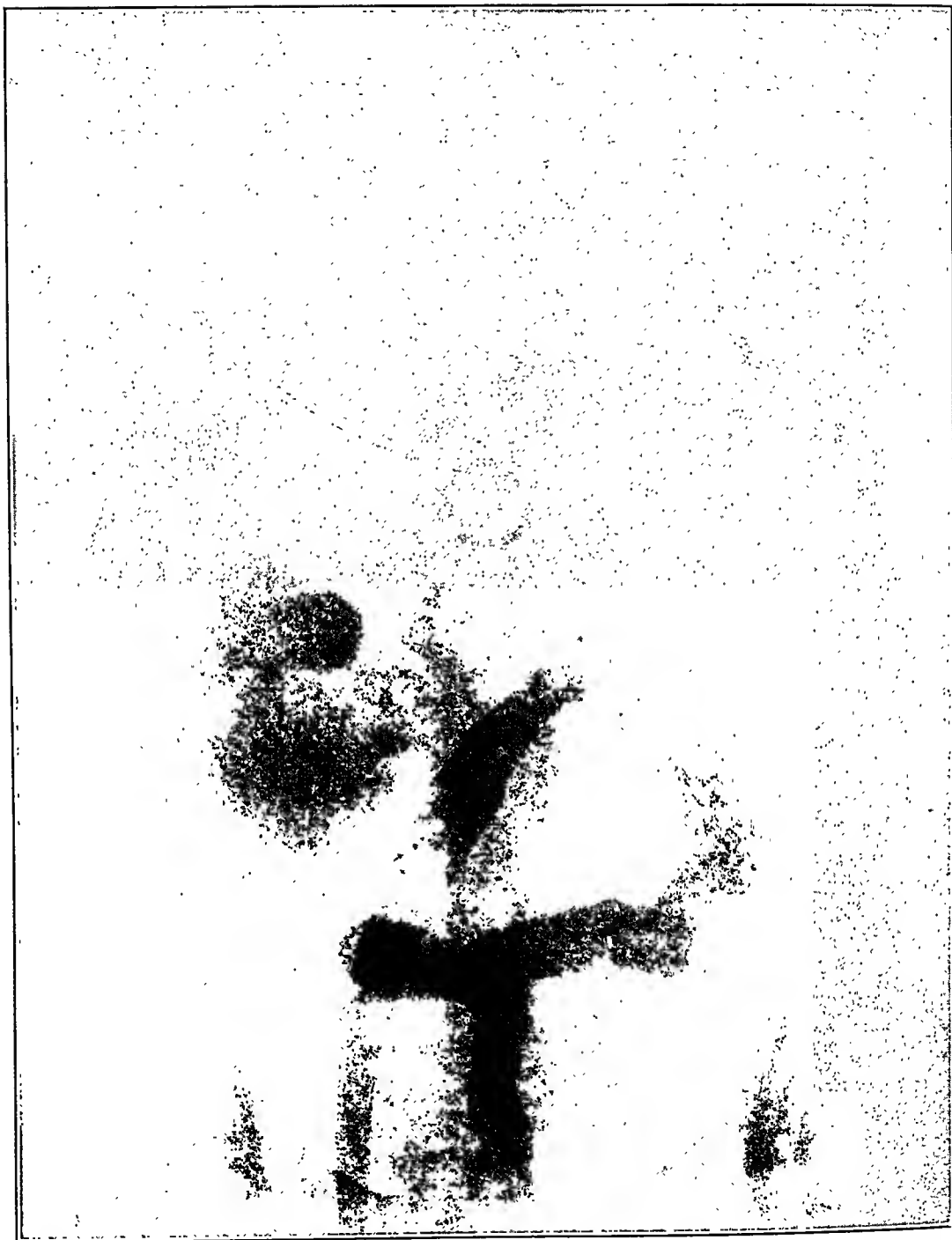


FIG. 2. Case I. This film was taken a short time before operation. Shows very much dilated cecum which gave a great deal of pain and which was in reality a large abscess cavity.

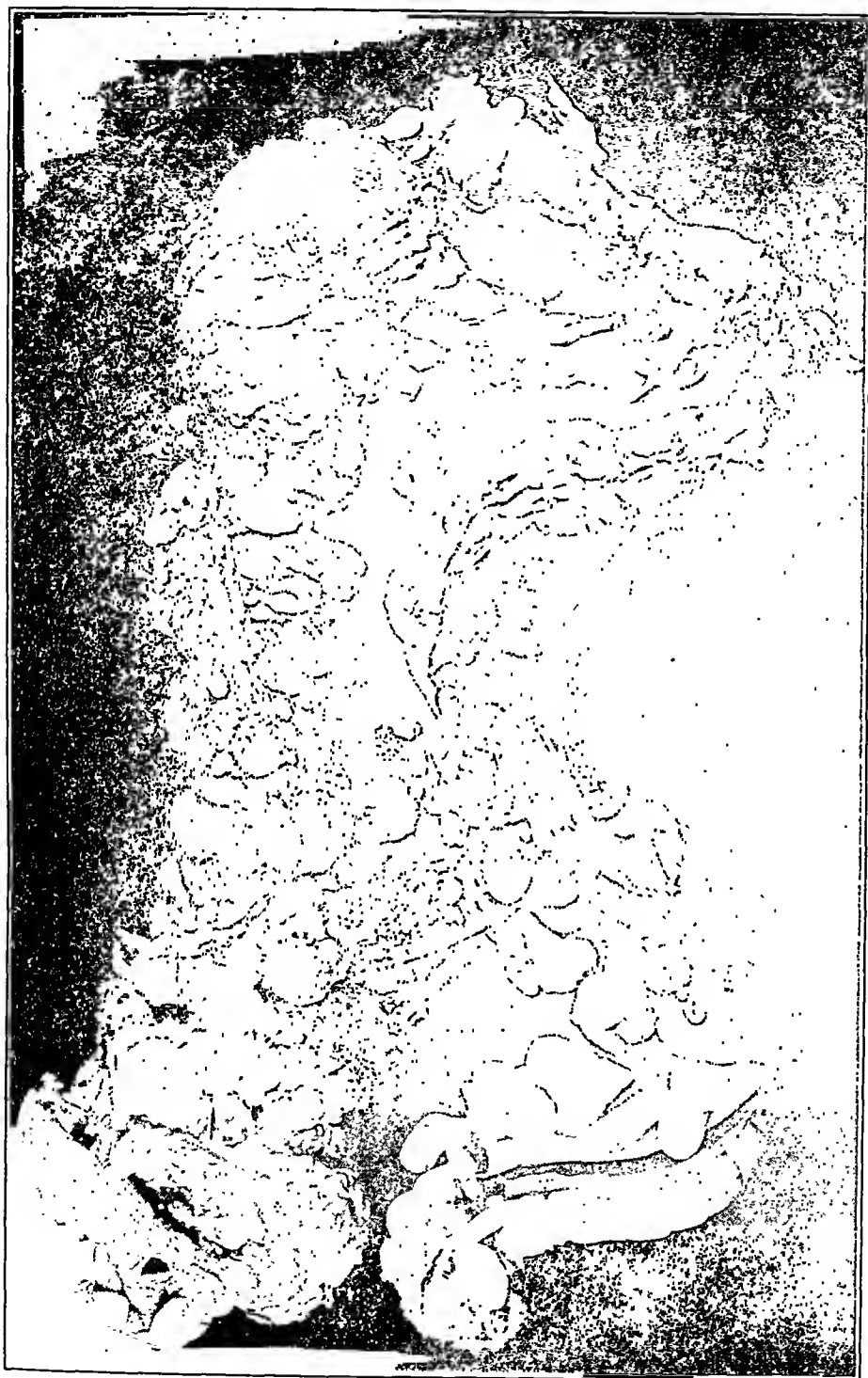


FIG. 3. Case I. The complete specimen showing the shrunken contracted condition of the colon and fatty epiploica.



FIG. 4. Case I. Transverse colon spread apart to show the hemorrhagic condition of the mucosa and the thick fatty layer between the mucosa and the muscular wall.

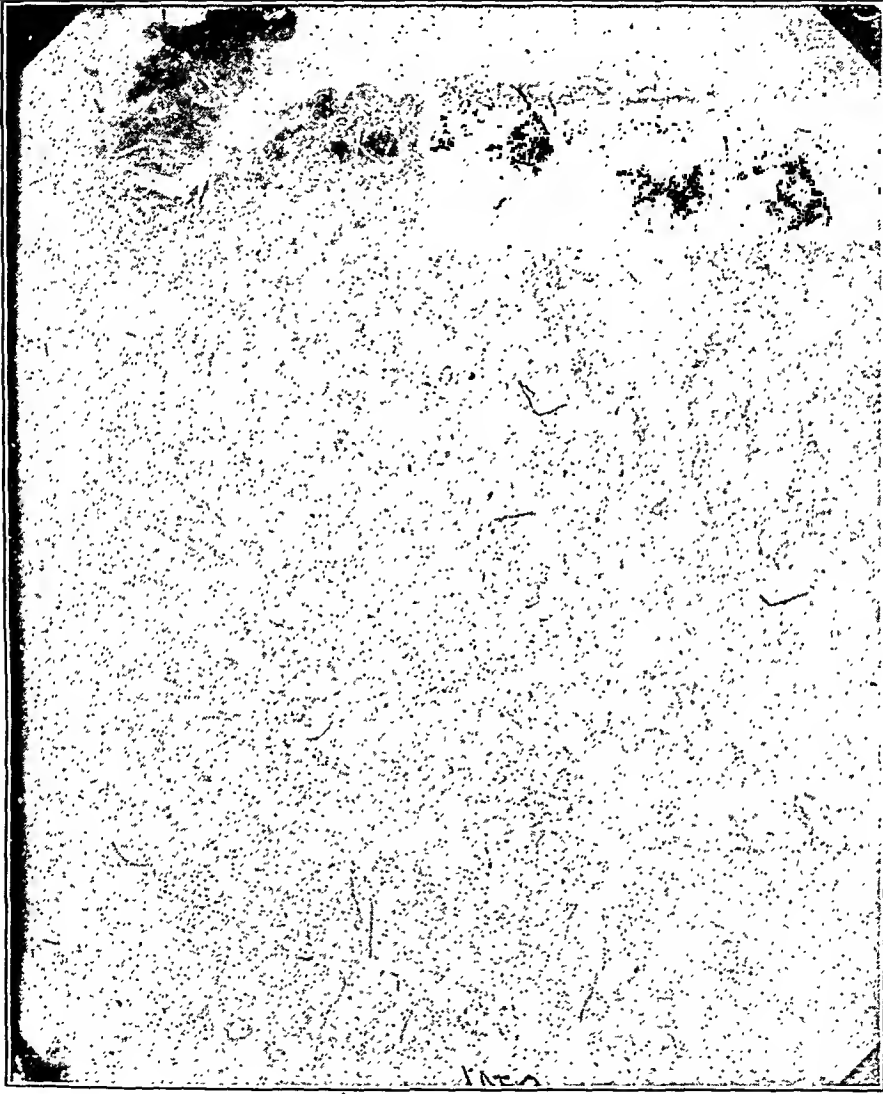


FIG. 5. Case 1. Section through wall showing the relative thickness of the mucosa, fatty submucosa and the muscular coat.



FIG. 6. Case I. Low power of the mucosa showing atrophy and ulceration of glandular epithelium, the acute exudate on the surface and the plasma cell reaction in the mucosa.



FIG. 7. Case I. High power showing acute inflammatory reaction on the surface and the plasma reaction in the mucosa.



*Case II.*—Female, age 26. Came under observation Feb. 19, 1920. Gave a history of diarrhea of one year's duration. Diagnosis of exudative colitis was made together with severe form of secondary anemia. Spleen was not enlarged. Normal weight 125, present weight 87½ pounds. General condition very poor. March 5, 1920 Dr. Harvey G. Mudd operated upon her. Cecum found to be very much thickened and involved in the inflammatory process. Appendix also much thickened. Appendix removed. Ileum then brought up and a portion about four or five inches from the ileo-cecal valve was fastened to the wound. She improved very much in her general condition after the ileostomy until the latter part of the following August when she had a very acute attack with extension of the process into the ileum. She died of acute enteritis.

*Case III.*—Female, age 25. Came under observation Feb. 8, 1926. Had had diarrhea for nearly a year, recently blood and pus appeared in the feces. Her normal weight was 137 pounds, when she came under observation 116¾ pounds. Her spleen was definitely enlarged. Blood test showed severe secondary anemia. X-ray showed that the colon was involved to the splenic flexure. Procto-sigmoidoscopy revealed characteristic picture of ulcerative colitis. Entire bowel atonic in character. She was put on mercurochrome and high vitamin diet. Had very little appetite and soon developed fever. Sent to St. Luke's Hospital. She was greatly prostrated, ran very high temperature curve, ranging between 102-105. Mercurochrome had to be discontinued because of her inability to retain it. Was delirious and very ill. Finally determined on ileostomy. Dr. Vernon Mastin performed the operation March 19, 1926. Terminal ileum was definitely involved in the inflammatory process. The ileostomy opening was made six inches from the distal end of the ileum. Patient succumbed seven days later from peritonitis. This was a severe acute fulminating case.

*Case IV.*—Male, age 56. Came under observation April 25, 1921. Colitis seven years' duration. Often had thirty movements daily.

X-ray examination showed the loss of haustra in the colon characteristic of chronic ulcerative colitis. In May 1921 the operation of ileostomy was performed. The ileum was severed from the colon and the distal end was closed near the ileo-cecal valve. Proximal end brought through the muscle and fixed. He gained in weight and made considerable improvement. Did not have much trouble with the ileostomy opening. In June 1924 X-ray films showed colon to be extremely narrow excepting the cecum which was dilated. He was having at this time considerable pain in this region because of insufficient drainage. He continued to grow weaker and finally succumbed in June 1926 to perforation and peritonitis. Colectomy might have saved this patient but his general condition did not warrant it. The double opening in the ileum is to be preferred because drainage of the cecum is necessary.

*Case V.* Female, age 32. Came under observation Nov. 5, 1923. Gave history of colitis of twelve years' duration. In 1914 appendicostomy was done which appeared to make her much worse. In 1916 ileostomy was performed under Dr. Bertram Sippy's direction. The rectum was so contracted that it would not retain the barium enema. Barium was injected through the ileostomy opening and part of the colon visualized. Her general condition was very satisfactory. She was not suffering any pain and the ileostomy opening was functioning very satisfactorily. Feces analysis showed that the ileum was not involved in the inflammatory process. She consulted me in regard to colectomy. I advised against it and furthermore advised her not to attempt any irrigation of the colon but to let it alone.

*Case VI.*—Male, age 17. Came under observation May 13, 1925. X-ray films and proctosigmoidoscopy showed picture of chronic ulcerative colitis. Two years duration. Recent exacerbation of the condition with blood and pus mixed with the feces. Treatment consisted of high vitamin diet, insufflations of Scarlet R and calomel and bismuth powder and mercurochrome keratin coated tablets. In November Lugol's solution was



FIG. 8. Case II. Patient succumbed to enteritis six months after ileostomy.

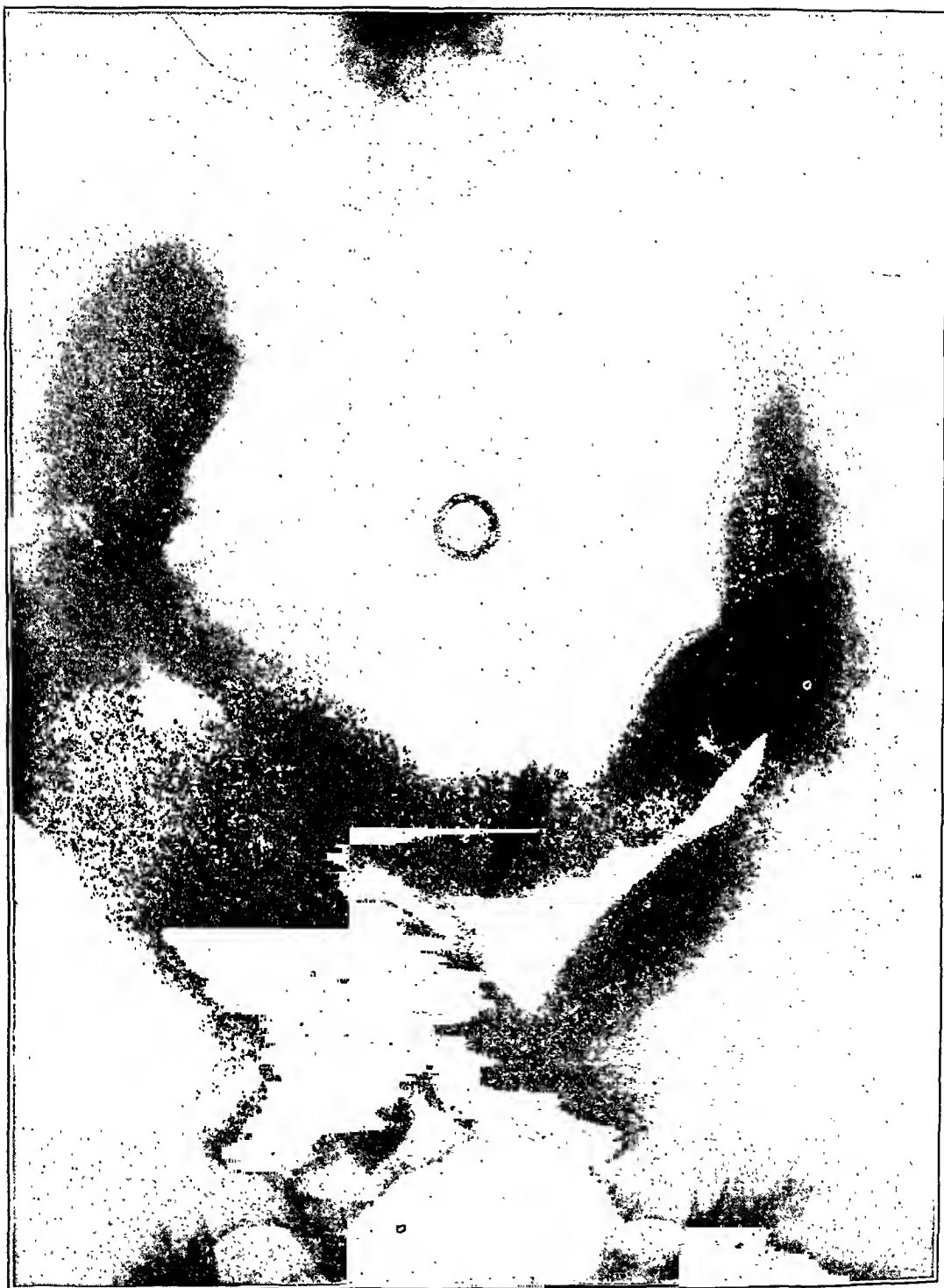


FIG. 9. Case III. A fatal case of the fulminating type of ulcerative colitis.



FIG. 10. Case IV. This film shows the condition when patient came under observation in April 1921.

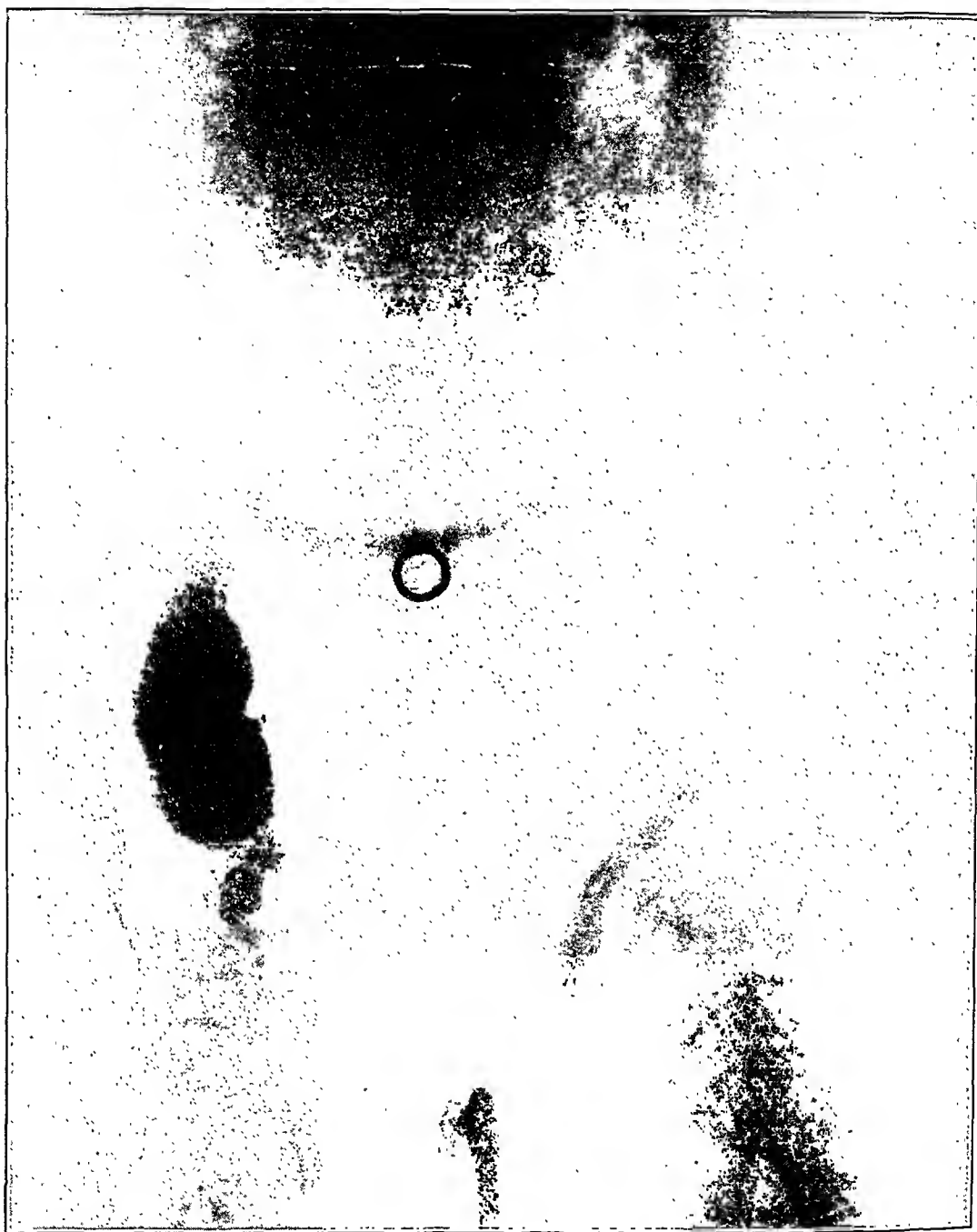


FIG. 11. Case IV. This film was taken three years after the operation of ileostomy. Note the narrowing of the entire colon except cecum which is dilated.

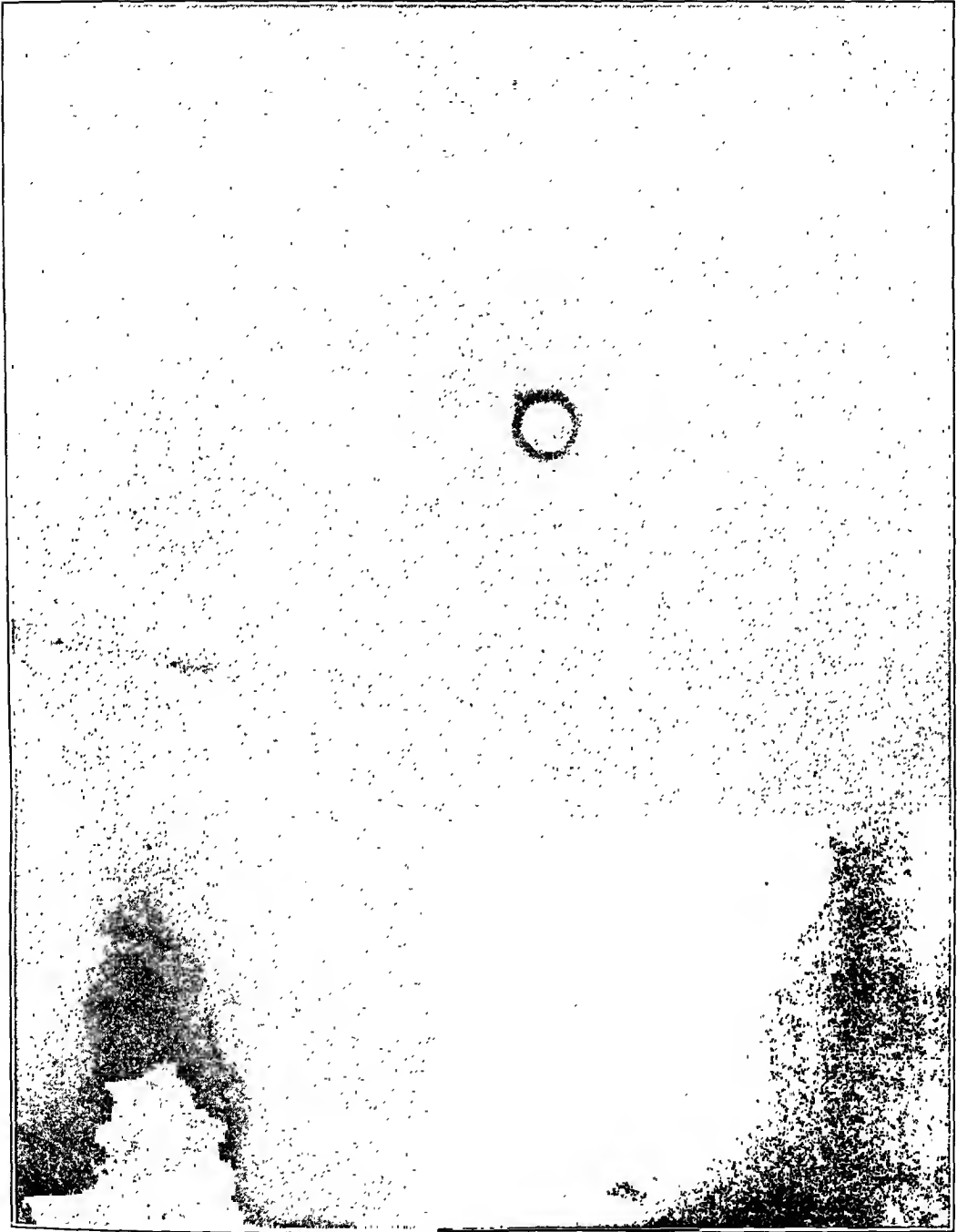


FIG. 12. Case V. The distal colon and rectum was obliterated seven years after ileostomy.

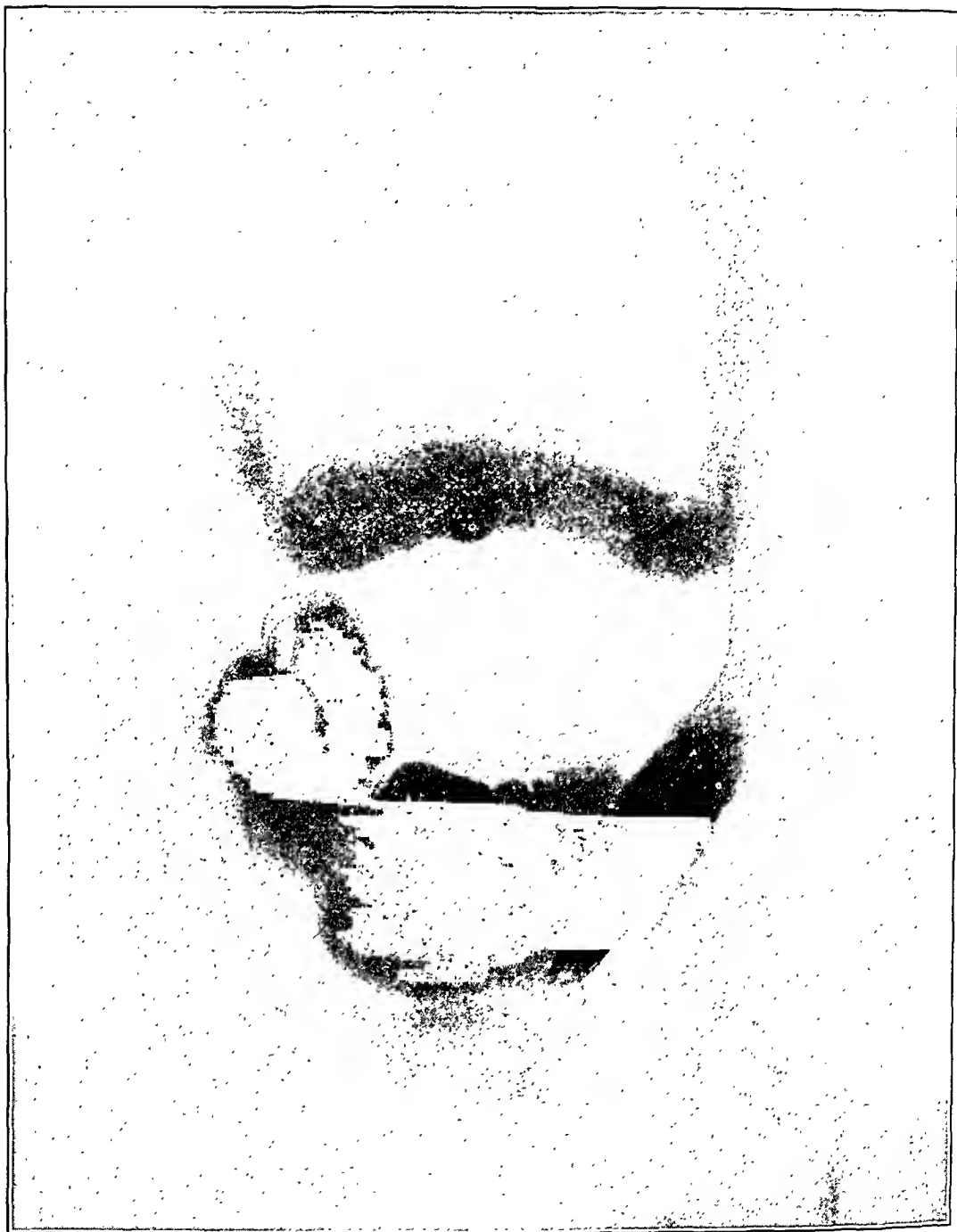


FIG. 13. Case VI. (May 15, 1925) Showing chronic ulcerative colitis involving entire colon.

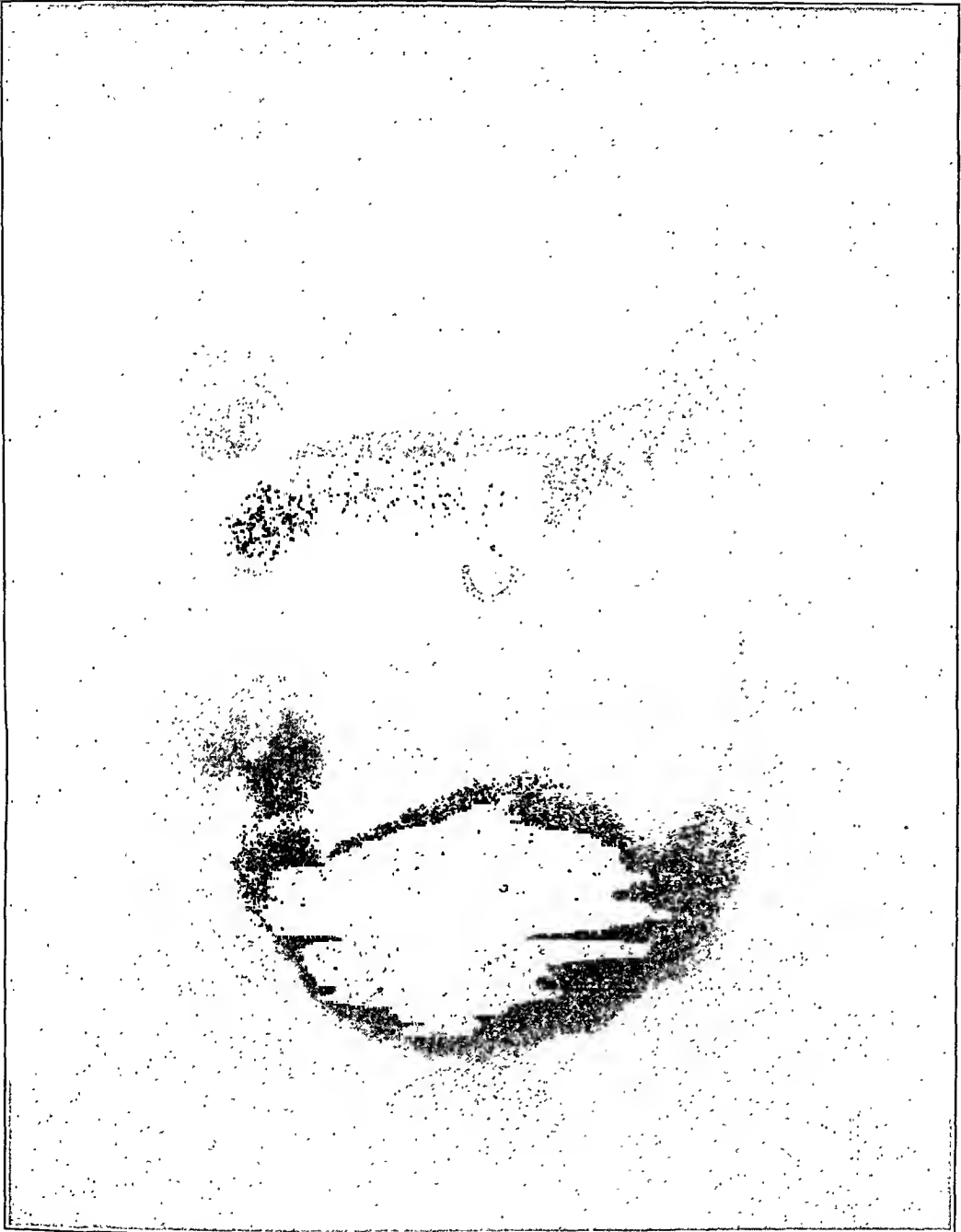


FIG. 14. Case VI. (July 20, 1926) Possibly slight improvement as shown by the wider transverse colon and possibly some increase in calibre of the descending colon.



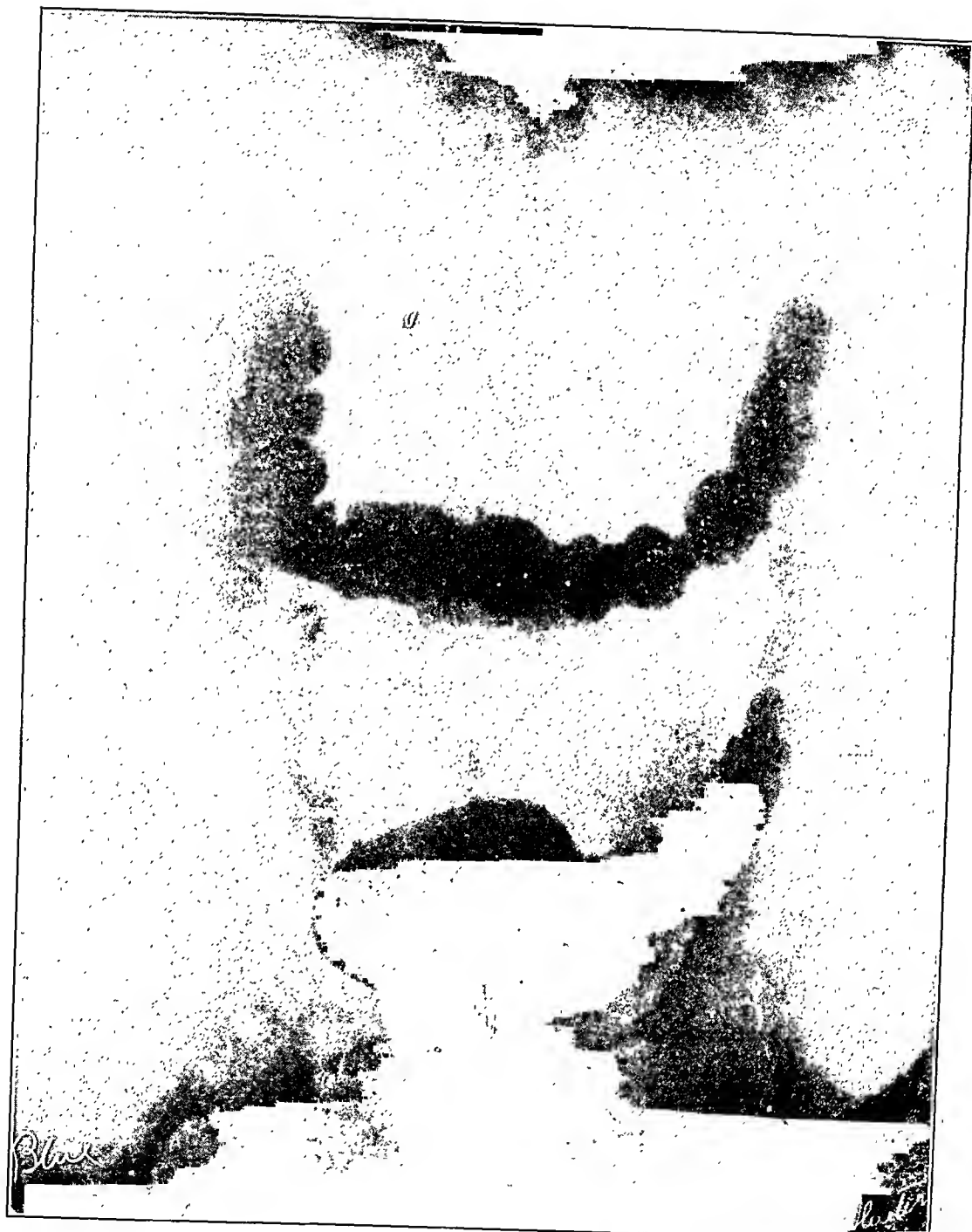


FIG. 16. Case VII. Shows marked improvement after high vitamin diet (May 11, 1926).



FIG. 17. Case VIII. A case of ulcerative colitis limited to the rectum and pelvic colon.



FIG. 18. Case IX. Colon was found to be involved from the anus to the splenic flexure. All the films were essentially the same as this one.

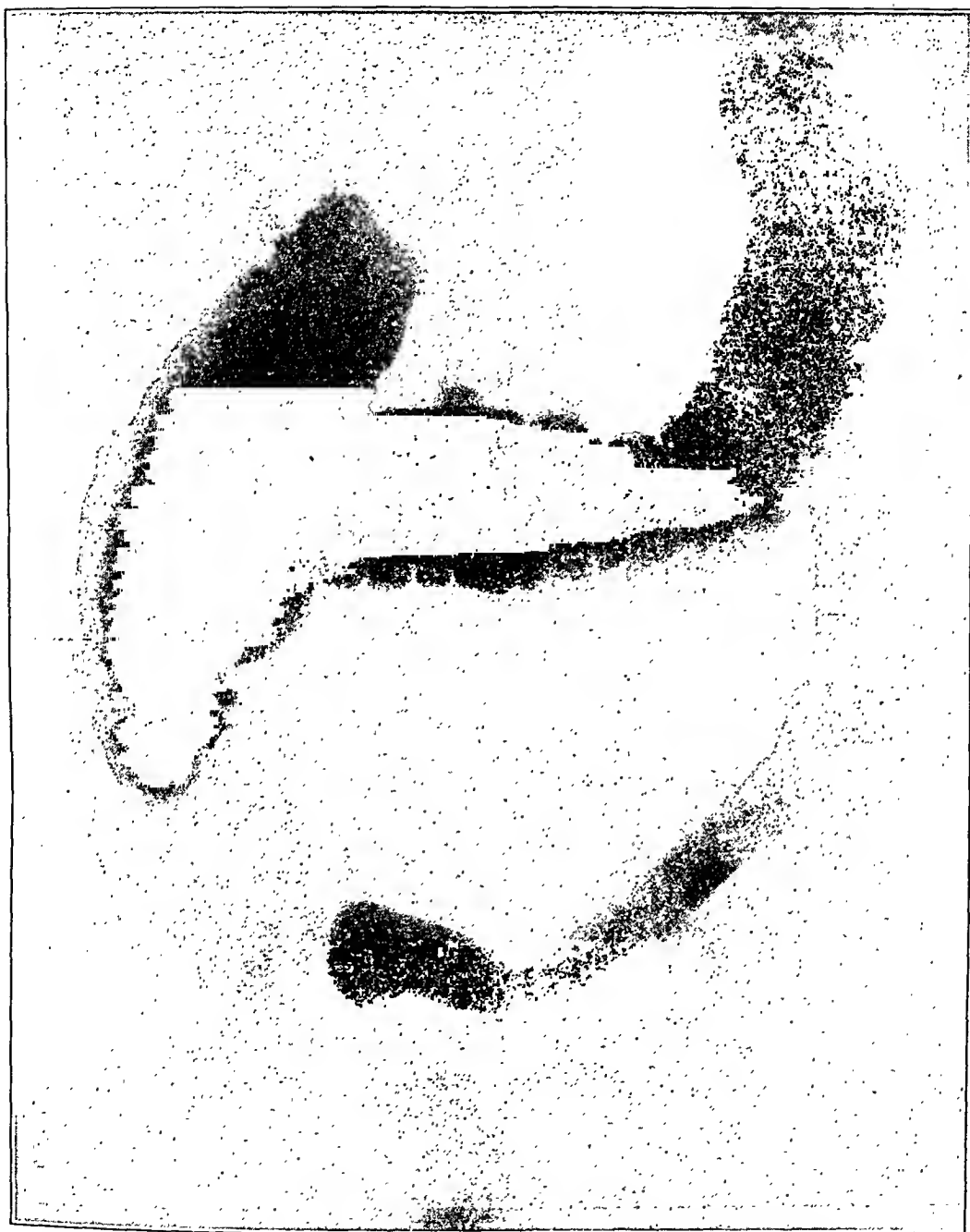


FIG. 19. Case IX. Just above the transverse flexure is one of the mercurochrome tablets not yet dissolved in the stomach.



FIG. 20. Case IX. Colonic insufflation. Note that the haustra are visible in the transverse colon, the narrow descending and iliac colon showing the absence of haustration characteristic of ulcerative colitis. Note here the collection of fecal matter in the transverse colon. The patient had not been taking bismuth. This case illustrates what Dr. Mills designated as peripheral colonic motility.

mouth and calomel powder. Bargaen's diplococcus was finally isolated and vaccine filtrate prepared. In November she had adenitis involving the posterior cervical glands. High temperature 103. Again sent to Jewish Hospital. Her glandular enlargement subsided within a week's time. She was given another blood transfusion and discharged from the hospital. There was no exacerbation of the colitis during this acute attack. Feces analysis taken recently showed a few clumps of mucus, no blood or pus cells. At the present time she appears to be perfectly well. The membrane shows characteristic pitting of healed ulcerative colitis. She has continued to gain in weight and strength.

*Case XI.* Female, age 18. Entered Jewish Hospital Nov. 10, 1926. Had suffered from bloody diarrhea of three weeks' duration. Past history essentially negative. Examination showed poorly nourished, sallow complexion. Tonsils out, heart and lungs negative, tenderness in left lower quadrant. Sigmoidoscopy showed typical picture of ulcerative colitis. Temperature runs from 101-103. Pulse from 110-140. Gastric analysis showed achylorhydria. Stool examination shows watery stools with considerable blood, pus and mucus. Urinalysis showed trace of albumin, otherwise negative. Blood picture is that of secondary anemia. Differential count normal. She was given blood transfusion, Bargaen's vaccine filtrate and high calorie, high vitamin fiber free diet. She made no response to treatment. Finally sigmoidoscopy revealed the presence of numerous polyps in upper rectum and pelvic colon. X-ray plate revealed a polypoid condition. Ileostomy has been done recently and she is now showing rapid gain in weight and strength. Colectomy will be advised later because the proctosigmoidoscope reveals several polypi that are already ulcerated and probably undergoing malignant degeneration. (Ileostomy was done by Dr. S. E. Newman).

*Case XII.* (Courtesy of Dr. Larimore) Female, age 16. Entered Barnes Hospital Sept. 9, 1925. Onset of present illness Feb.

1925. Abdominal discomfort which gradually became pain. Sigmoidoscopy revealed the presence of a normal rectum and pelvic colon. Gastro-intestinal X-ray examination showed contractural narrowing of the ascending and the transverse colons (more especially the proximal portion), and abnormal rugae markings of the descending colon. The changes in the more distal abnormal portions are probably of the same process less advanced, i.e. smaller, more sessile polyps. Diagnosis: Polyposis of the colon, benign. Operation by Dr. Evarts A. Graham. The transverse colon exhibited several small white nodules on the surface and the cecum showed gross evidence of disease. The sigmoid was practically normal. The colon was resected, including three inches of the ileum down to the middle portion of the sigmoid. The ileum was sutured to the sigmoid, over a rubber tube inserted through the rectum from below. Tube pulled down, inverting ileum into the sigmoid according to the Balfour method. The patient withstood the operation well. Pathological report, "The material consisted of a cecum, the ascending colon, transverse colon, and most of the descending colon, a meter in length. The cecum was normal and beginning at a point 4 cm. above the ileo-cecal valve were three irregular long ulcers extending to within 7 cm. from the end of the specimen. Each of these seemed to follow a muscle band. In addition, scattered here and there, over the mucosa were smaller, irregular ulcers. Lymph nodes seen on the outside of the intestine were enlarged but showed no gross change beyond a chronic inflammation. The mucosa itself showed the folds greatly exaggerated and numerous small polypi were seen. Microscopic Report: The sections showed large intestine in which there was thickening in most places of the submucosa and marked infiltration of all the layers with round cells. The mucosa especially was filled with these cells. In addition, there was increased vascularity and all the vessels were filled with blood. In places the epithelium was missing and was replaced by areas of necrotic cells and polymorphonuclears and round cells. No evidence of any specific process was seen. There was some increase in the size of



FIG. 21. Case X. When patient first came under treatment.



FIG. 22. Case X. Shows increase in the caliber and length of the cecum. Patient now clinically well.





FIG. 23. Case XI. This plate shows remarkable view of the polypoid condition (Dr. Newman secured this plate by a special technic in which the colon was not distended by the barium enema).

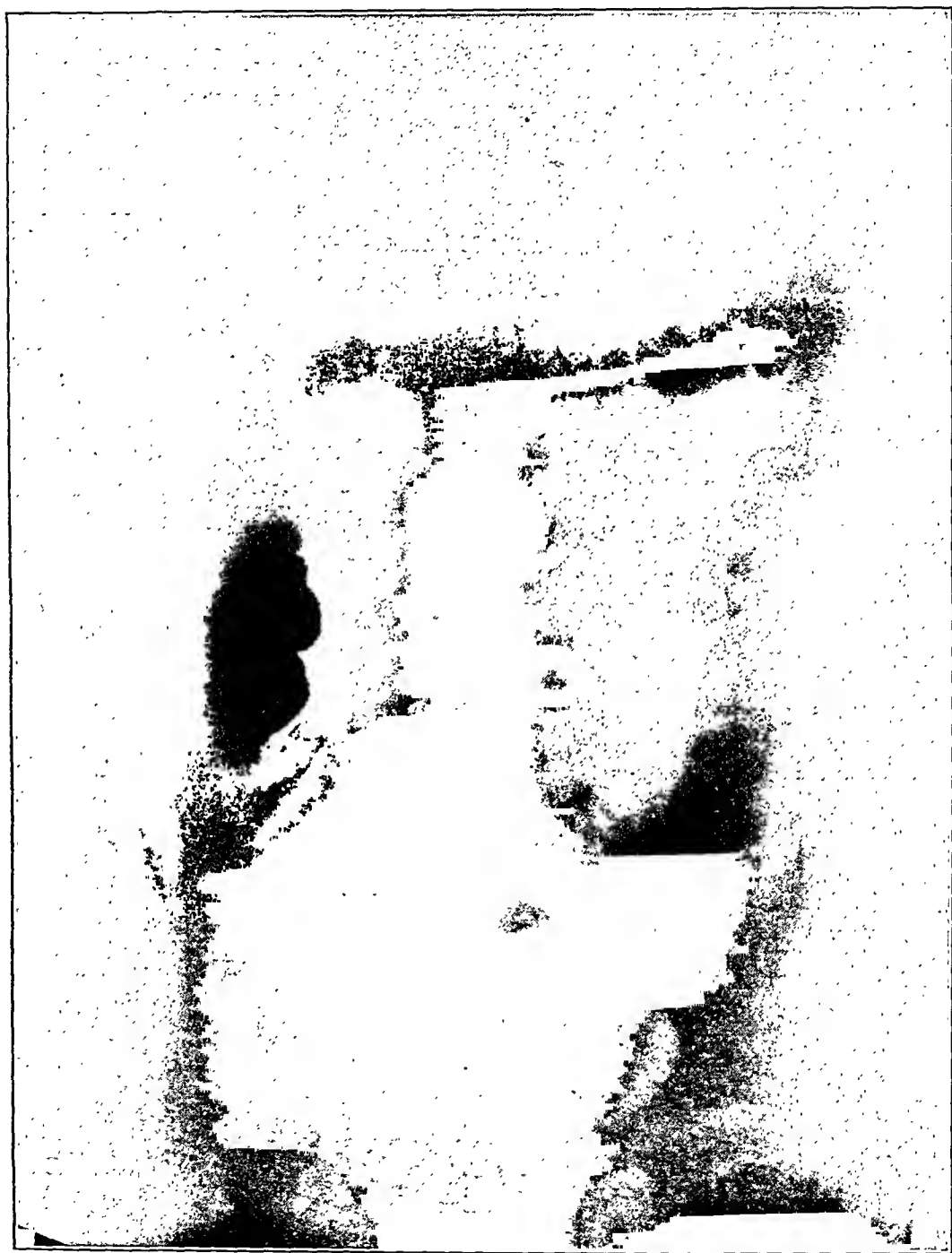


FIG. 24. Case XII. Polyposis of the colon. Note irregularities particularly in the transverse colon.

the mucosal folds. Diagnosis: Chronic Colitis. Polyposis of the colon.

This patient had a difficult post-operative course. She developed a fecal fistula. She was capricious with her diet and otherwise obstructive and wholly unco-operative to medical care. Her condition became progressively worse and death occurred at about five months post-operative. The diagnosis of the colonic pathology in this case depended entirely upon the roentgenological findings. This was supported and the clinical status of the condition determined by the persistent occult blood reaction of the stools and by the secondary anemia.

*Case XIII.* Female, age 42. Came under observation June 25, 1923. Case of healed ulcerative colitis discovered accidentally in course of examination. Patient came in suffering from constipation and functional disturbances. No evidence of any organic trouble. Proctosigmoidoscopy revealed a membrane having the appearance of healed ulcerative colitis. However, she gave no history of diarrhea or dysentery. I take this to be probably a case that occurred early in life and that completely healed and gave her no further trouble except constipation from the narrowed colon.

*Case XIV.* Male, age 62. Came under observation May 11, 1925. Duodenal ulcer patient. Gave no history of dysentery. X-ray enema showed loss of haustration of the pelvic colon. Sigmoidoscopy showed granular areas and pitting characteristic of ulcerative colitis. The colitis might have occurred in very early life and healed without any subsequent attacks.

*Case XV.* Male, age 54. Came under observation Nov. 3, 1911. Had repeated attacks of hemorrhagic proctosigmoiditis. X-ray plate showed normal colon, no deformity characteristic of ulcerative colitis.

*Case XVI.* Male, age 61. Came under observation May 23, 1921. Lues of the colon.

*Case XVII.* Male, age 34. Came under observation Nov. 6, 1926. Amoebic dysentery of six months' standing. Note that

there is no loss of haustration and that the colon shows contractures here and there.

## CONCLUSION

Bargen's diplococcus is the primary etiologic agent in the production of chronic ulcerative colitis. It must be differentiated from chronic catarrhal form which appears to be a separate disease entity.

The pathology needs revision and further study. The thickening of the wall and contraction of the lumen of the gut does not appear to be due to a true fibrosis. One of our cases revealed a tremendous infiltration of fat in the submucosa.

The autogenous vaccine therapy did not give good results in our series of cases. The best results were secured by hospitalization, blood transfusions, mercurochrome by mouth and rectal injections, and intensive local treatment of lesions in the rectum and lower colon during the convalescent stage. Relapses are frequent and spontaneous cure unquestionably occurs.

Ileostomy should be postponed until all methods of treatment have failed. It is a life saving measure when the lower colon contracts to such a degree that sufficient passage of fecal matter is no longer possible. After ileostomy the colon continues to contract and may be finally obliterated. The cecum dilates and perforation and peritonitis will result if the drainage through the ileostomy opening is insufficient. In cases of this class colectomy is advisable.



FIG. 25. Case XIII. Case of healed ulcerative colitis. Accidental discovery.

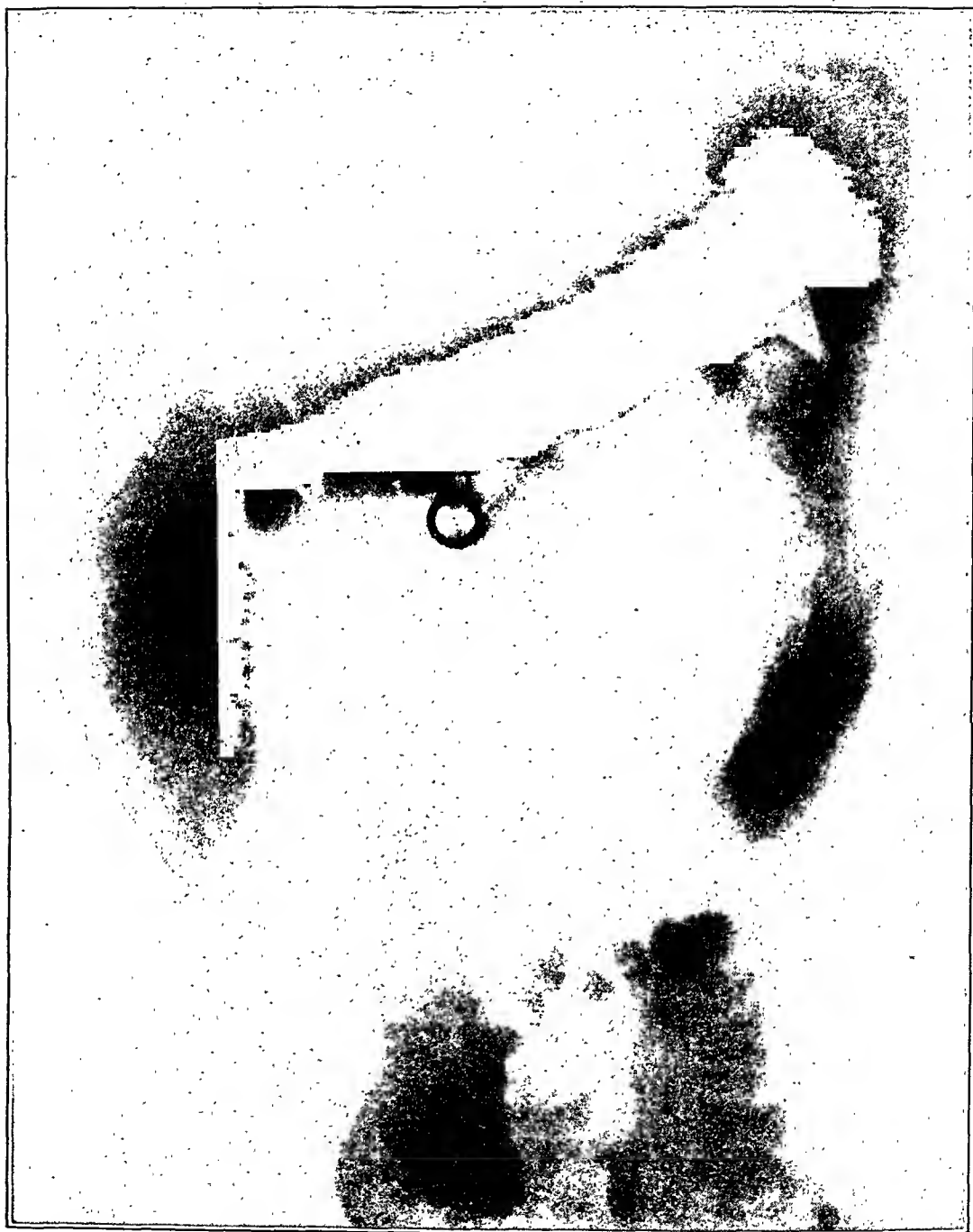


FIG. 26. Case XIV. Case of healed ulcerative colitis. Accidental findings.

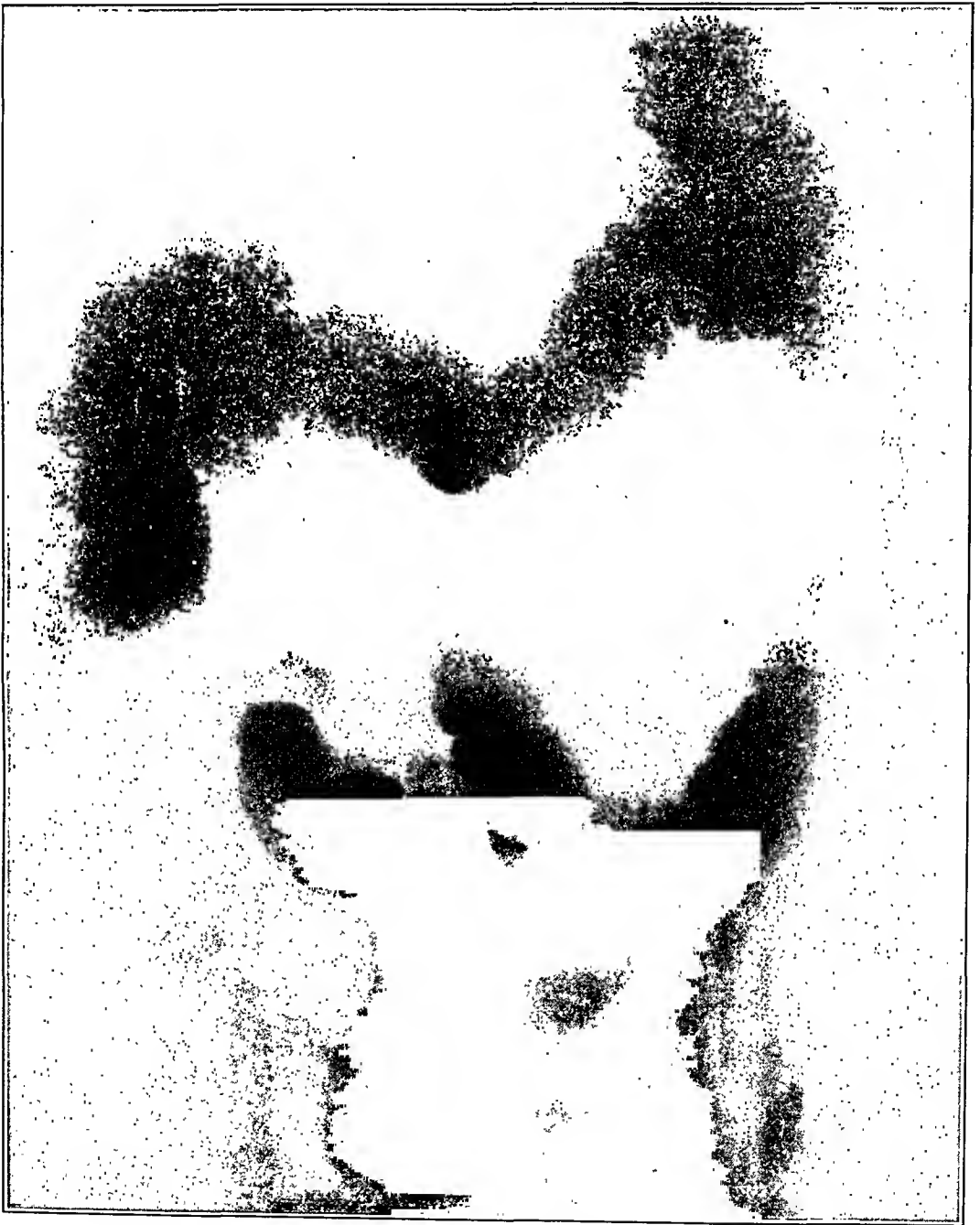


FIG. 27. Case XV. Luetic colitis involving iliac and pelvic colons.



FIG. 28. Case XVI. Case of repeated attacks of hemorrhagic proctosigmoiditis. Normal colon.

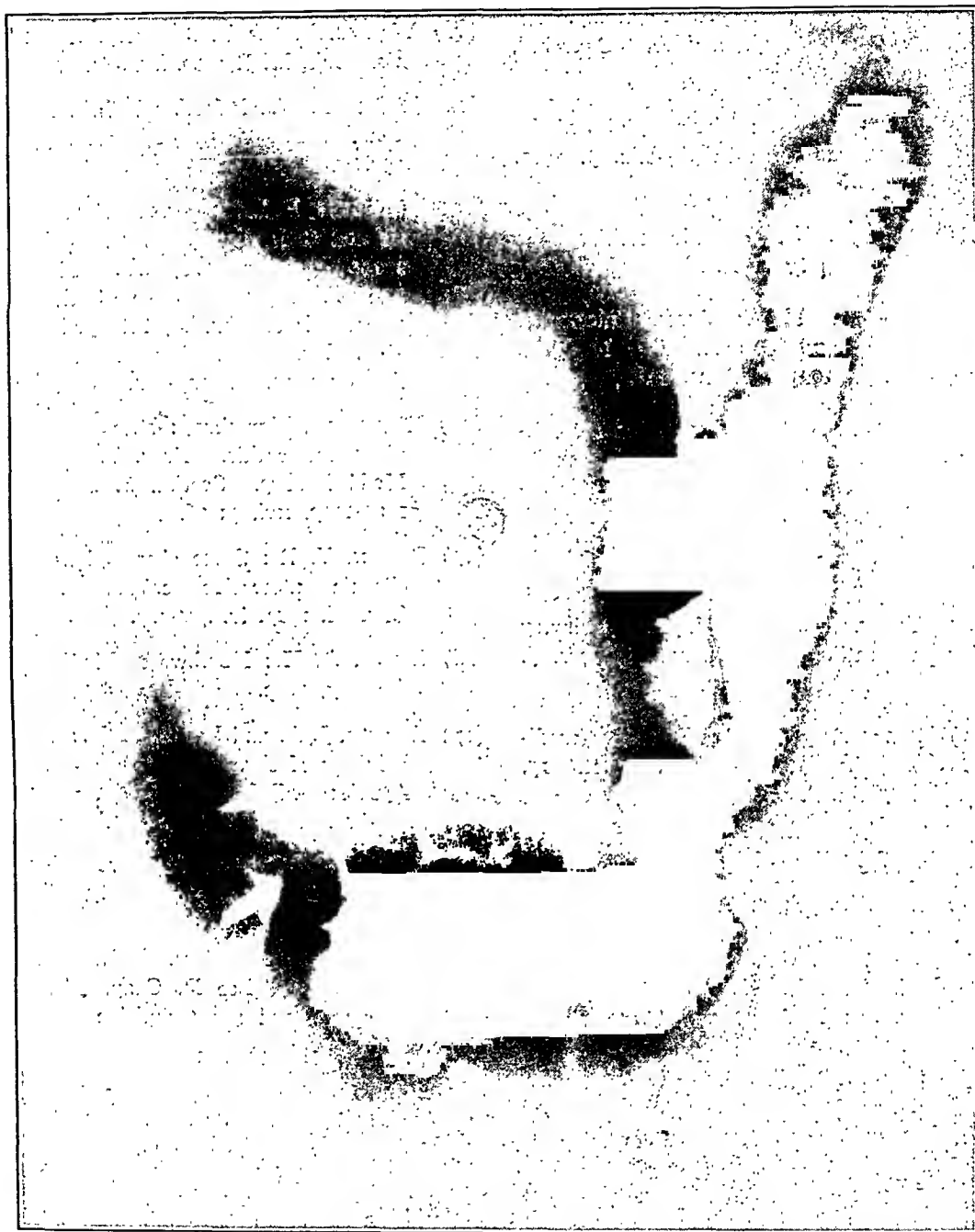


FIG. 29. Case XVII. Amoebic dysentery six months duration. No loss of haustration.



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## Editorials

### United States Public Health Service

*The Surgeon General Reviews World Health Conditions and Summarizes His Work in Annual Report.*

AN ACCOUNTING of the health of the people of the United States in so far as Federal duties and responsibilities are concerned is given in the Annual Report of the Surgeon General of the Public Health Service, which has just been transmitted to Congress. This is the Report for the 129th year of the existence of the Service.

The Surgeon General says that through modern developments in public health organization—national and international—it is now practicable for the country to keep informed of the prevalence of epidemic diseases and of the health of populations throughout the world. This knowledge is of considerable importance in preventing the introduction of dangerous communicable diseases into the country from abroad.

Health conditions generally throughout the world were better during the year ended June 30, 1927, than for any previous year on record. The first half of the year was characterized by unusually low death rates in foreign countries. The most serious condition that interposed to prevent even lower mortality rates was the epidemic of influenza which affected a considerable area of that part of the world.

Bubonic plague, which, by reason of its wide geographic distribution and the method of its spread, remains one of the major quarantinable diseases, continued to be pandemic, but was less prevalent than it has been in recent years. India remained the principal focus of infection, that country having over nine-tenths of the cases reported throughout the world.

Asiatic cholera, which is still a great scourge in India, showed no decrease there, and appeared with more than usual prevalence in the countries eastward as far as Korea and Manchuria.

It is an interesting commentary on the advancement of modern sanitary science that yellow fever—a disease the very name of which not so long ago terrified even the people of this country—was practically confined to one section of the continent of Africa during the year under report. With the exception of one case which occurred at Bahia, Brazil, in July, 1926, the disease was not reported in the Western Hemisphere.

The devastating epidemics of typhus fever which swept Russia after the World War have definitely passed, although the disease remains endemic in that region. There was no marked spread of the disease during the year.

The health of the people of the United States was generally good during the year ended June 30, 1927, as

compared with preceding years. The death rate for all causes for the calendar year 1926 in 28 States was 12.1 per 1,000 population. This was slightly higher than the rate for 1925, which was 11.7. The increase was probably caused principally by the large number of deaths from respiratory diseases. This country escaped the epidemic of influenza which swept over Europe during the winter of 1926-27, and the few cases reported here were mild. Typhoid fever declined during the calendar year 1926, and the case and death rates for diphtheria for the year were the lowest ever recorded. This disease showed a small increase, however, during the first part of 1927. The general downward trend in diphtheria is undoubtedly the result of the use of antitoxin and toxin-antitoxin immunization.

The death rate from tuberculosis continued its decline, and heart disease, diabetes, and nephritis, which had been increasing in recent years, showed lower rates than were expected.

Smallpox decreased during the calendar year 1926. In most sections of this country the disease was of mild type, but in some localities it existed in severe form. Out of a total of 30,450 cases of smallpox reported during the year from 41 States, there were 380 deaths. The disease was the most fatal on the Pacific Coast, which section reported only one-fifth of the total number of cases, but two-thirds of the number of deaths. In view of the demonstrated protective value of vaccination, the Surgeon General says that it is difficult to explain why this simple preventive measure is not universally employed.

Although endemic foci of the important quarantinable diseases continued to exist abroad, no cases of cholera, yellow fever, or bubonic plague gained entrance to the country during the year. Two cases of plague were apprehended aboardship at the United States quarantine station at New Orleans, La., and 17 cases of smallpox and 2 cases of leprosy were detected at domestic quarantine stations. The discovery of three cases of plague among rats at Los Angeles, Calif., however, indicates that the disease continues to exist among rodents; and it persists especially among ground squirrels in certain sections of California, and requires vigilance on the part of the health authorities concerned for the protection of the human population.

The geographical prevalence of tularemia, a disease identified a few years ago by an investigator of the Public Health Service, was discovered during the year to extend to 10 additional States, increasing the area of known distribution of this new disease to 36 States, the District of Columbia, and Japan.

Rocky Mountain spotted fever is another disease being studied by the Public Health Service, the knowledge of the area of prevalence of which is being extended. This disease originally reported by only two Western States, was reported last year from nine states.

The infant mortality rate (deaths of infants under one year of age per 1,000 live births), considered an important index of the efficiency of public health work, has been decreasing for many years. The rate for 28 States in 1926 was 72.8, as compared with 71.5 for 1925, both of which rates are ex-

tremely low as compared with rates of a few years ago (about 100 in 1915).

The work of the Public Health Service in preventing the introduction of diseases from abroad involves both control at domestic ports and medical inspections at certain foreign ports. At domestic ports during the year, 20,284 vessels, 820,793 passengers, and 1,140,922 seamen were inspected by quarantine officers; at insular ports, 2,991 vessels, 169,461 passengers, and 226,373 seamen were inspected; and at foreign ports, 5,954 vessels, 424,172 passengers, and 272,872 seamen were inspected prior to embarking for the United States. A total of 7,116 vessels were fumigated, either because of the occurrence of diseases aboard or for the destruction of rodents. Thirty-one thousand and seventy-three rats were recovered, of which number 18,334 were examined for plague infection.

The medical examination, by Public Health Service medical officers, of applicants for immigration visas in foreign countries of origin, first inaugurated in 1925, in England, Scotland, and Ireland, was extended during the past year to Germany, Sweden, Norway, Poland and Denmark. The advantages of the system to the prospective immigrants, to the communities of origin, and to the transportation companies resulted in additional requests to the State Department for the extension of the plan to other countries. During the year medical examination of applicants for immigration visas were being made by Public Health Service officers at 20 American consulates in eleven countries. Out of 148,539 applicants examined during the year, 12,-

974, or 8.75 per cent, were found to have mental or physical disabilities; 6,580, or 4.43 per cent, were refused visas for medical reasons.

At domestic ports 881,699 alien passengers and 996,317 alien seamen were examined under the immigration law, by medical officers of the Public Health Service, and of this number 24,292 passengers and 3,117 seamen were certified for various diseases and disabilities coming under the law.

Investigation was made of the typhoid fever epidemic in Montreal, Canada, with the permission of the Canadian authorities, and a report was made regarding the cause of the epidemic and recommending precautionary measures.

Aid was given the local authorities in the localities of Florida devastated by the hurricane of September, 1926, and the Public Health Service cooperated with the States and the American Red Cross in the emergency relief work in the Mississippi flood area. Within ten days from the beginning of the flood emergency, 14 Public Health Service officers trained in emergency health work and familiar with the localities affected by the flood, were in the field to assist the State Health authorities. Arrangement has also been for a continuance of this cooperation in providing public health protection to the inhabitants of the devastated areas during the period of rehabilitation.

The Public Health Service continued to provide medical and hospital treatment of sick and injured American merchant seamen and other Government beneficiaries—the oldest function of the Service and the specific purpose for which it was organized under the

act of July 16, 1798, 129 years ago—and probably at no time during this period has the aid thus given by the Government to American merchant vessels been of greater value or of more importance in keeping the American flag on the seas.

More than 300,000 beneficiaries apply annually at 152 ports of the United States and its insular possessions where marine hospitals and relief stations are maintained for the giving of hospital and out-patient treatment and making physical examinations. There were 1,288,061 hospital days' treatment given, mostly to merchant seamen and Coast Guardsmen, and 632,341 separate out-patient treatments were supplied. The American seamen are the principal beneficiaries, receiving 67.4 per cent of all the hospital treatment furnished. The Coast Guard furnished 14 per cent of the clientele, while the Employees' Compensation Commission constitutes about one-fifth of the total of the Service beneficiaries.

Because of the exceptional facilities offered in the hospitals of the Public Health Service for the study of syphilis and gonorrhea, important investigations were undertaken, at the marine hospital at New York, of more effective methods of prevention and treatment. Over a period of many years about 20 per cent of all patients treated by the Service were ill as the result of venereal diseases. In 1926, however, this percentage was slightly lower, the rate being 17.

As evidence of the extent of anti-venereal disease work during the nine years since the Division of Venereal Diseases was established, 3,105,952 cases of venereal diseases have been

reported by the State boards of health, nearly 800 venereal disease clinics have been established by various agencies at which 1,023,326 patients have received 16,330,994 treatments, 62,595 lectures have been delivered to a total of 8,530,000 persons, and 34,676,512 pieces of educational literature have been distributed.

The investigations of public health problems continued during the year. The investigations of stream pollution have been of great practical benefit in determining the limitations of natural and artificial purification of polluted water. The malaria studies have demonstrated the possibility of airplane control of mosquitoes in otherwise inaccessible areas by spreading larvicidal dust. Various inquiries were made in the study of health problems in industry. Other public health problems investigated include child health, posture studies, the advantage of exercise to health, and industrial morbidity.

In investigations of the diseases of man, an extremely important function of the Public Health Service, studies have continued on pellagra, the timely results of which have had a valuable application in the flood area, and on tularaemia, tuberculosis, Malta fever, typhus fever, trachoma, pneumonia, encephalitis lethargica, Rocky Mountain spotted fever, syphilis, goiter, influenza, and leprosy.

Further studies on narcotic drug addiction indicate a reduction in the number of habitues, and confirm the opinion previously arrived at that addiction is, in general, a symptom of neuropsychopathic make-up.

In a survey of salt-marsh mosquitoes conducted in cooperation with the

Bureau of Entomology, it was found that although there are nearly 6,000,000 acres of salt-marsh along the Atlantic and Gulf Coasts, the acreage requiring mosquito control can be expressed in tens of thousands.

It has been the long-standing policy of the Public Health Service to cooperate with official and unofficial bodies for the advancement of the public health. Some of the work is specifically required by law; the remainder is sanctioned by efficient health administration. The volume of cooperative work conducted during the fiscal year was extensive, and included practically all the departments and some independent establishments of the Government.

In the field of international developments, the year was marked by two important international official conferences for the improvement of existing treaties or conventions regulating maritime procedures. The representatives of 60 Governments, including the United States, met during the year at Paris to revise the International Sanitary Convention of Paris (1903, 1912), which was necessitated by recent advances in medical science. A conference of the directors of health of Pan American Governments was held in Washington, under the chairmanship of the Surgeon General as director of the Pan American Sanitary Bureau, during which constructive progress was made in matters pertaining to Pan American public health and sanitation.

Among the recommendations made by the Surgeon General in his annual report, he commends a bill introduced in the last Congress for the coordination of public health activities of the Government, which provides for a grant of authority to the President to transfer to the Public Health Service any executive agency (other than those in the War and Navy Departments and those in the Veterans Bureau) when such transfer is deemed to promote greater efficiency in the conduct of public health work. The bill also provides for details of officers of the Public Health Service to other executive agencies, upon request of the heads of departments or independent establishments; for the extension of research through close cooperation with educational and research institutions by an enlarged hygienic laboratory; and for the coordination of research of public-health officials and scientific workers. Provisions were also contained for unification of terms of appointment of personnel, with compensation and tenure assured to scientific and professional workers adequate to attract to the service, men and women of proved qualifications; and for the enlargement of the present advisory board for the hygienic laboratory into a national advisory health council. The Surgeon General believes that such a coordination of public health activities would tend to eliminate duplication of effort in administration, research, and educational measures, and would prove a decisively forward step in public health in the United States.

## Abstracts

*Hypertension of the Pulmonary Circulation. Its Causes, Dynamics and Relation to Other Circulatory States.* By ELI MOSCHOWITZ (Amer. Jour. of Med. Sc., Sept. 1927, p. 388).

Hypertension of the lesser circulation is common. It passes generally under the name of "pulmonary congestion," "right-sided insufficiency," or arteriosclerosis of the pulmonary vessels." It is caused by any lesion that increases the peripheral resistance within the lesser circulation. The most common causes are mitral disease, especially mitral stenosis, emphysema, whether primary (senile) or secondary (asthmatic), infiltrating lesions of the lung (chronic tuberculosis with induration, bilateral pleural synechiae, chronic interstitial pneumonia, tumors), kyphoscoliosis, patent ductus arteriosus and communications between the two sides of the heart. A sustained hypertension of the lesser circulation leads to arteriosclerosis of the pulmonary vessels. A "primary" sclerosis of the pulmonary vessels, if it exists at all, is extremely rare. There is an interdependence in the incidence of arteriosclerosis of the greater and lesser circulations. The compensatory dynamics following hypertension in the lesser circulation are described. The physical signs of hypertension in the lesser circulation are those brought about by the compensatory mechanism. In the main these are: Increased venous pressure, accentuation of the second pulmonic sound, dilatation and hypertrophy of the right heart, dilatation of the pulmonary conus, cyanosis, dilatation of the superficial veins (especially pectoral), enlargement and tenderness of liver, lowered kidney function and infarction of the lungs. It is the hypertension and not the arteriosclerosis that is responsible for this clinical syndrome. As in the greater circulation, it is the disturbed function and not the anatomic sequence that

is at fault. A transient (usually) terminal hypertension of the lesser circulation arises under a number of other conditions. In general vascular hypertension, hypertension of the lesser circulation may follow mitralization, when myocardial insufficiency sets in and when there is an associated emphysema. This explains, in part, the difference between the pale and the cyanotic hypertensive. In left coronary artery disease hypertension of the lesser circulation arises only after myocardial insufficiency sets in. The so-called "Ayerza's disease" is not a disease, but a syndrome developing from any lesion that causes hypertension and consequent arteriosclerosis of the lesser circulation. The constant relation of syphilis to this disease is not proven. Edema of the lungs may either follow or cause hypertension of the lesser circulation. Changes in cardiac rhythm cause hypertension of the lesser circulation only when myocardial insufficiency arises. There is a likelihood that cirrhosis of the liver associated with cardiac disease is the result of the increased venous tension within the hepatic area and of an hepatic arteriocapillary fibrosis. Hypertension of the lesser circulation may be the mechanism of the hitherto unsatisfactorily explained cyanosis in congenital heart disease.

*An Experimental Study of Diathermy, IV. Evidence for the Penetration of High Frequency Currents Through the Living Body.* By RONALD V. CHRISTIE AND CARL A. L. BINGER (Four. of Exper. Med., November 1, 1927.)

In this fourth paper on an experimental study of diathermy the principles governing the passage of high frequency currents through various conductors are discussed and exemplified in the experiments done on both non-living and living bodies. It is

shown that the current takes the path of least electrical resistance rather than the shortest path, and the maximal heating occurs at the point of greatest concentration of the lines of the current flow. In a homogeneous medium with parallel electrodes maximal heat production occurs in those portions of the medium adjoining the electrodes and the heat gradient is from without inward. Under these circumstances maximal heating never occurs at the center. In discussing the localization not only the electrical resistance and current concentration, but also the cooling effect must be considered. In experiments on the dog's cavader no evidence of the so-called "skin effect" could be demonstrated. This is in contradistinction to the findings of Bertman and Crohn, but the discrepancy is explained on the ground of a technical error in their work. The finding of no "skin effect" is in harmony with the conclusions of Donne and Tredell, based on both experimental and theoretical considerations. As the result of experiments on the anesthetized dog, the conclusions drawn were: 1st. The heat gradient of the body is reversed during diathermy and heating occurs from without inward. 2nd. Deep heating during diathermy is greater than that which results from the application of local heat to the skin. 3rd. The lung can be heated by diathermy in spite of simultaneous cooling of the chest wall. The authors regard their experiments as giving satisfactory evidence of the passing of the current through the interior of the body.

*Degenerative Changes in the Germinal Epithelium in Acute Alcoholism and their Possible Relationship to Blastophthoria.* By CARL VERNON WELLER (Trans. of the Assoc. of Amer. Physicians, Vol. xlii, p. 277, 1927).

Weller has studied the pathological changes occurring in the testes of nine cases of acute alcoholic intoxication, all of them being coroner's cases in which death occurred during, or immediately after severe alcoholic intoxication. One of these, in a boy of 17 years, was a first experience; the others

were probably an exacerbation of a more or less chronic or intermittent alcoholism. In all of these cases the germinal epithelium showed marked parenchymatous degeneration, leading when sufficiently marked to total aspermatogenesis, the various orders of maturing cells disappearing in an inverse order to that of their production and the basal layer of cells alone remaining to afford the possibility of regeneration if the individual survives. In the testes showing less marked degeneration there is an apparent increase in spermatocytes and spermatids, with very few tailed spermatozoa, as if there had been an inhibition in the final steps of spermatogenesis. With somewhat more marked changes the germinal epithelium becomes thinner than normal, perhaps only two to four cells thick. At this stage there are but few spermatids, and the spermatogonia and spermatocytes take on a marked degree of vacuolation, which may have a zonal distribution in the tubal epithelium, the spermatids next to the lumen escaping. A typical cell division forms, teratocytes are numerous, appearing as mutinucleate masses near the lumen, apparently spermatids which have accomplished nuclear division only, and giant nuclear forms which are found especially in the deepest layer of the germinal epithelium next to the basement membrane. Finally the epithelium becomes reduced to one or two rows only, and no evidence of spermatogenesis is present. That portion of the germ plasm which is in process of maturation is especially susceptible. The survival of the, as yet, undifferentiated primary germinal epithelium makes possible the restoration of spermatogenic function following nonlethal intoxication. The changes found are in no sense specific for alcoholic intoxication, precisely similar ones are found clinically in a great variety of conditions, particularly in epidemic pneumonia, and they can be duplicated in animals in experimental lead poisoning. There is no proof that alcohol acts directly upon the testis; while this seems probable the primary changes may be elsewhere. Such blastotoxic conditions, particularly the alcoholic because of its frequency, become of great bio-



logic and clinical importance. The testicular changes found are in excess of those which it is necessary to produce experimentally in order to demonstrate a deleterious blastophthoric effect by breeding experiments. It is certain that in the earlier stages spermatozoa capable of giving rise to defective off-spring must be set free. It follows that procreation during a period of intoxication entails a definite hazard as to the quality of the off-spring which may result. It has been shown that this applies to lead poisoning as well as to alcoholism, pneumonia, typhoid fever, certain dietary deficiency diseases, exposure to certain forms of radiant energy, etc., a list which is being constantly increased. Thus this conception of the liability of the germ plasm is capable of extensive practical eugenic application.

*Antirachitic Value of the Sun's Rays Through Various Special Window Glasses.*

BY FREDERICK F. TINSDALE AND ALAN BROWN (Amer. Jour. of Diseases of Children, November, 1927, Vol. xxxiv, p. 742).

This research was carried out under a grant from the Department of Health of the Province of Ontario. Three glasses: 1. Vitaglass, manufactured in England, 2. Vioray glass, 3. Corning Special glass, which have been claimed will transmit the antirachitic rays of sunshine were experimentally tested out with animals placed on a rachitogenic diet (McCullum's). As a result of their experiments these investigators concluded that the antirachitic effect of the sun's rays (including skylight) through Vitaglass, Vioray glass and Corning special glass is from 25 to 50 per cent of the antirachitic effect obtained without the use of glass. Obvious differences could not be detected in the efficiency of the three glasses. No antirachitic effect, or at most a negligible one, is produced by the sun's rays through ordinary glass. The antirachitic effect of skylight through an ordinary window glazed with Vioray glass is slight—in fact almost negligible except immediately adjacent to the window. Similar results were obtained with rays through an open window covered with ordinary fly screen.

In order to obtain much benefit from rays through an open window, or a window glazed with special glass, it is necessary to receive the direct rays of the sun. The use of special glass during the winter months is probable of little value. Its use is justified in the latitude of Toronto from about the first of March on, as the inclement spring weather prohibits the exposure of patient to the sun's rays which at that time have a great antirachitic effect.

*The Incidence of Scarlet Fever Streptococci in Throats of Diphtheria Patients.*

BY PAUL S. RHOADS (Jour. of Infectious Diseases, November 5, 1927, p. 377).

In spite of the most rigid precautions against cross infections scarlet fever sometimes develops in patients admitted to diphtheria wards. Councilman, Mallory and Pearce in a study of 220 deaths from diphtheria found scarlet fever 34 times. It has long been known that streptococci could be cultured from the complicating lesions of diphtheria more often than any other micro-organism. Until methods of recognizing the scarlatinal streptococci have been worked out, it was impossible to know how many of the complications were due to scarlatinal infection. Interest in the problem was stimulated by the observation that occasionally a diphtheria patient who reacted positively to the Dick test on admission, became negative before leaving the hospital without developing a recognized rash. At times such patients have desquamated. The question naturally arises whether or not these may have been diphtheria patients or diphtheria carriers who were at the same time suffering from throat infections due to scarlet fever streptococci, but without a rash, or having a rash so transient that it was not observed. That scarlatinal throat infection may occur without eruption has long been suspected by clinicians. Dick and Dick showed experimentally in 1921 that such infections do occur. In 1925, Williams using the toxin neutralization method described by Dick and Dick identified 42.8 per cent of hemolytic streptococci from excised tonsils as well as one strain from the sputum of a

patient with bronchitis and one from an osteomyelitis lesion as scarlatinal strains. Stevens and Dochez using the same method found 5 scarlatinal strains in the 17 hemolytic streptococci tested. These strains came from the throats of nurses with acute pharyngitis during an outbreak of scarlet fever in the nursing group. With agglutination and agglutinin absorption methods their percentage of scarlatinal strains was slightly higher. Nicholls studied 21 strains from sources other than scarlet fever patients, most of them from patients with tonsillitis, pharyngitis or sinusitis. Using the toxin neutralization method ten of these were identified as scarlatinal strains. Rhoads' study was that of the incidence of hemolytic streptococci in the throats or noses of 100 patients admitted with a diagnosis of diphtheria to Chicago hospitals for contagious disease, and then to determine which of the hemolytic strains were scarlatinal or non-scarlatinal by the toxin neutralization method. As a result of this study hemolytic streptococci were cultured from the throats or noses of 29 of a series of 100 patients

who were admitted with the diagnosis of diphtheria to hospitals for contagious disease in Chicago. Sixteen or 55.2 percent of these strains of hemolytic streptococci were identified as scarlet fever streptococci by the toxin neutralization method. The strength of the scarlatinal toxin produced by these strains varied from 100 to 10,000 skin test doses per cc. It was less than 2,000 skin test doses per cc. in 14 of the 16 strains. Thirteen, or 44.8 per cent, of the strains of hemolytic streptococci isolated did not produce any demonstrable scarlet fever toxin. It is possible, therefore, that infection with scarlet fever streptococci of comparatively low toxin production may account for the development of a negative Dick test during the course of acute infections diagnosed clinically or culturally as diphtheria. It is possible that some of the cases reported were scarlet fever occurring in diphtheria carriers and diagnosed diphtheria because of positive cultures. The results reported indicate the advisability of individual isolation to prevent cross infection with hemolytic streptococci in diphtheria wards.

## Reviews

*The Methods of Clinical Diagnosis.* By ALEXANDER GEORGE GIBSON, M.D., F.R.C.P., AND WILLIAM TREGONWELL COLLIER, M.D., M.R.C.P., 398 pages, 4 plates. Longmans, Green & Co., New York, 1927. Price in cloth, \$5.00.

The object of this book is to supply the student with a short practical guide to the fundamentals of disease. The aim of the book throughout is to give a knowledge of the technique of examination, what to look for and how to look for it. The student is asked to recognize the importance of a routine examination of the patient from top to toe. More errors are due to the omission of some part of the examination than to misinterpretation of the signs discovered, and although in the stress of practice some part of an examination may have to be discarded, it can never be discarded safely. From this point of view the book has been divided into two sections, the examination of regions and the examination of systems, so that a general review of the whole body should be carried out before attention is concentrated on the system believed to be primarily affected. The authors have also endeavored to emphasize the importance of the simpler methods of examination. Percussion and auscultation should always follow not precede inspection; instrumental and laboratory methods should always come last. For this reason they have added to each system an outline of symptoms, since in many cases more is to be learned from the history than from physical examination. An attempt is made to teach the student the habit of making inferences from what he sees, and therefore of making provisional diagnoses as he goes along, which may be dealt with when all the evidence of the examination is available. If the student studies the methods by which the most skilled of his teachers arrive at a

diagnosis he will be struck by the stress laid on certain parts of the examination and the slight attention paid to others. This art of knowing what to omit is the result of prolonged experience, and a conscious or unconscious judgment in what is important and what is trivial. This may appear to be an intuitive gift, but it cannot be developed apart from practice. The student is advised to read first the examination of Regions; the chapters dealing with Systems should be read in conjunction with actual cases. The consideration of Chapters I and II may be left until the technique has been mastered. In dealing with clinical pathology the aim has been to give one reliable method rather than a choice, and to restrict all methods to those that can be done by the student or practitioner himself without access to a well-equipped laboratory. There are seventeen chapters, the first four dealing with an elementary introduction concerning aims of diagnosis and nature of disease, the general methods of diagnosis, general features of the patient and the examination of regions; the remaining chapters deal with the various systems. This is a very good manual for the student who is taking his course in physical diagnosis; it will also be a great aid to him during his internship, and will aid the general practitioner by refreshing his mind in regard to matters of technique and conditions that should be looked for.

*The Normal Diet.* A Simple Statement of the Fundamental Principles of Diet for the Mutual Use of Physicians and Patients. By W. D. SANSUN, M.S., M.D., F.A.C.P., Director of the Potter Metabolic Clinic, Department of Metabolism, Santa Barbara Cottage Hospital, Santa Barbara, California. Second edition. 136 pages.

C. V. Mosby Company, St. Louis, Missouri. Price in cloth, \$1.50.

The author has for many years given the subject matter of this book in lecture form to patients suffering from the various nutritional disorders. Since diet errors are very common, and such errors are undoubtedly responsible for many minor ailments, as well as for some of the more serious ones, he believes that a simple statement of the fundamental principles underlying the selection of a normal diet may fill a definite need. Normal diet menus are given as well as special menus to illustrate how such diets may be built without violating any of the fundamental principles. Chapter II treats of the bulk requirements of the body, Chapter III of the acid-ash type of acidosis, Chapter IV of the acetone type of acidosis, Chapter V of the caloric requirements of the body, VI of the protein requirements, VII of the mineral, VIII of the vitamins and IX of the water requirements. This little volume is devoid of fads, and the material given is consistent with our scientific knowledge of the subject. It is simply and clearly written, and is a book of value for the household as well as for the hospital diet kitchen.

*The Diabetic Life. Its Control by Diet and Insulin.* A Concise Practical Manual for Practitioners and Patients. By R. D. LAWRENCE, M.A., M.D., M.R.C.P., (London); Chemical Pathologist and Lecturer in Chemical Pathology, King's College Hospital. Third edition. 185 pages, 11 illustrations. P. Blakiston's Son and Company, Philadelphia, 1927. Price in cloth, \$2.50.

A third edition of this work has been called for within a year of the appearance of the second. During this time there have been no revolutionary ideas promulgated concerning insulin or the treatment of diabetes. New practical details have, however, been incorporated in this edition as the result of increased experience, and a full explanation of the mode of insulin action and the ketone ratio have been added. The object of the book is to bring the modern

treatment of diabetes by diet and insulin within the scope of the general practitioner and the understanding of the patient, whose intelligent cooperation is necessary for the best results. Sufficient knowledge has accumulated to make it possible to lay down simple rules of treatment without being too dogmatic. By means of a simple yet varied and accurate diet scheme—the Line-ration diet—the busiest practitioner is enabled to start accurate treatment without any elaborate calculation of diets and food-stuffs. It is a book for both patient and doctor. The discussion of the theoretical basis of treatment has been made as short as possible, and the routine treatment has been dealt with in full practical detail. The book is, of course, written from the standpoint of insulin chiefly. It is, however, sufficiently comprehensive, is well written, and one of the best of the special manuals written upon the subject. It may be highly recommended.

*Diseases of the Skin.* By HENRY H. HAZEN, A.M., M.D., Professor of Dermatology in the Medical Department of Harvard University; Sometime Assistant in Dermatology in the Johns Hopkins University; Member of the American Dermatology Association. Third edition. 572 pages, 248 illustrations including two color plates. C. V. Mosby Company, St. Louis, 1927. Price in cloth, \$10.00.

The first edition of this book appeared in 1915, the second in 1922. This, the third edition, contains a number of radical changes. Diseases have been classified more accurately according to their etiology. In accordance with modern beliefs the word "Eczema" has been omitted. The subject of Anaphylactic Dermatitis has received considerable mention. The use of X-rays, radium, unipolar and bipolar fulguration and the Alpine lamp has been carefully revised. The bibliography has been omitted, but a number of new illustrations have been included; the great majority of the photographs were taken either in the author's own clinic or in that of Dr. Gilchrist. A

very large proportion of these illustrate skin diseases in the negro. The paucity of photomicrographic illustrations is notable. Many of the gross photographs are not very well produced, and from the standpoint of illustration this work is much inferior to other recent publications on Dermatologic affections. The text-material is also much reduced; some subjects are insufficiently treated. Syphilis is discussed from the dermatologic standpoint. The most individual thing about this book is that it offers an unusual amount of material concerning dermatologic conditions in the negro.

# College News Notes

## THE JAMES M. ANDERS TESTIMONIAL DINNER CELEBRATING HIS FIFTIETH ANNIVERSARY IN THE PRACTICE OF MEDICINE *Tuesday, November 29, 1927, at 7 o'Clock*

A testimonial dinner was given Dr. James M. Anders of Philadelphia on November 29 in honor of his fiftieth anniversary in the practice of medicine. Dr. Josiah H. Penniman, President and Provost of the University of Pennsylvania, presided at the dinner, which was attended by a large number of prominent members of the medical and legal professions. Dr. John B. Deaver, on behalf of those present, presented a life-size bust of Dr. Anders to the doctor.

Dr. Anders has the distinction of being the only individual on whom has ever been conferred Mastership in the American College of Physicians. As President of The College during 1922-23, and a member of the Board of Regents for three years, he rendered most valuable service in determining many of the present policies and principles of the organization.

He is an author and has long been active in civic and welfare work. From 1882 to 1916 he was professor of medicine and clinical medicine in the Medico-Chirurgical College of Philadelphia, and thereafter professor of medicine in the Graduate School of Medicine of the University of Pennsylvania. He is now a member of the Board of Managers of the Medico-Chirurgical and Polyclinic Hospitals, and a director of the Health Council and Tuberculosis Committee.

Dr. Anders is an ex-president of the Philadelphia County Medical Society, member of the Pennsylvania State Medical Association, fellow of the American Medical Association, ex-president of the American Climatological and Clinical Association, ex-president of the American Society of Tropical Medicine, ex-president of the American

Therapeutic Society and a member of the Alpha Mu Pi Omega medical fraternity.

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Dr. William R. Bathurst (Fellow, February 21, 1924), of Little Rock, Ark., is the newly elected President of the Southern Medical Association. Dr. Bathurst is a dermatologist who has distinguished himself not only in his own state but elsewhere. He is professor of dermatology at the University of Arkansas School of Medicine and a member of the staffs of St. Vincent's Infirmary, the General Hospital and the Missouri Pacific Hospital. In addition, he is editor of the Journal of the Arkansas Medical Society.

The Southern Medical Association will hold its Annual Meeting for 1923 at Asheville, N. C.

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### OBITUARY

Dr. Robert L. Crum died following a stroke of apoplexy on the 26th of October at his home in Los Angeles. Born in 1881, he received his medical education at St. Louis University. He was a member of the Hollywood Country Club, the University Club and of the Los Angeles County, California State and the American Medical Association. Since February 1920 he has been an Associate of the College. He was on the Staff of St. Vincent's and the Los Angeles General Hospitals. He was a Captain in the Medical Corps during the World War. He was a thirty-second degree Mason and a Shriner.

The members of the American College of Physicians and his many professional friends mourn the passing of a good physician.

# PRELIMINARY PROGRAMME FOR NEW ORLEANS MEETING

Preliminary program of the American College of Physicians for the meeting in New Orleans next spring, beginning March 5. The meeting will start on Monday, at 10 A. M. with the usual address of welcome from the Mayor of New Orleans; the President of Tulane, Dr. Dinwiddie; The President of the Orleans Parish Medical Society and Dr. C. C. Bass, Dean of the School of Medicine of Tulane University of Louisiana. Dr. Frank Smithies will give a reply to the address of welcome. The program will be continued as follows:

1. Dr. Julius Bauer, Vienna, Austria. (Title to be announced).
2. Dr. David P. Barr, "Multiple Myeloma."
3. Dr. L. G. Rowntree and Dr. George E. Brown, "Studies in Blood Volume with the Dye Method."

4. Dr. Joseph Sailer. Title to be announced.

5. Dr. Frank R. Menne, "The Effect of Iodine on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

## EVENING SESSION, MONDAY, 7:45

1. Dr. Maud Slye, "Cancer and Heredity."
2. Dr. J. L. Goforth, "Natural and Acquired Body Resistance to Neoplasia."

## TUESDAY MORNING, MARCH 6—10 O'CLOCK

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."
2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."
3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."
4. Dr. C. C. Sturgis, Dr. Raphael Isaacs and Dr. Millard Smith: "Treatment of Pernicious Anemia with Liver Fraction."

### Symposium on Tuberculosis.

5. Dr. Charles L. Minor. Title to be announced.

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

## EVENING SESSION—7:45 O'CLOCK

1. Dr. James S. McLester. Title to be announced.

2. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

3. Dr. T. Z. Cason, "Some Unfinished Research Problems of the South."

## WEDNESDAY MORNING, MARCH 7— 10 O'CLOCK

1. Dr. L. F. Bishop, "The Practice of Cardiology."

2. Dr. Morris H. Kahn, "Heart Strain and its Consequences."

3. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

### Symposium on Epilepsy

4. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

5. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

6. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

7. Dr. Tom Throckmorton. Title to be announced.

## EVENING SESSION—7:45 O'CLOCK

### Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."

4. Dr. J. C. Small, "Rheumatic Fever."

## THURSDAY MORNING, MARCH 8—10 O'CLOCK

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."
2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."
3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the View Point of an Internist."

## Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."
5. Dr. Frederick M. Allen, "Present Results and Outlook of Jealietic Treatment."
6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."
7. Dr. W. H. Olmstead. "The Dietetic Management of the Diabetic in the Doctor's Office."

## FRIDAY MORNING, MARCH 9—10 O'CLOCK

## Symposium on Tropical Medicine.

1. Colonel Roger Brooke. Title to be announced.
2. Dr. Aldo Castellani. Title to be announced.
3. Dr. Wm. M. Jones, "The Early Lesions of Intestinal Amebiasis."
4. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.
5. Dr. Aristides Agramonte, Havana, Cuba. Title to be announced.

## FRIDAY EVENING, MARCH 9—7:45 O'CLOCK

1. Dr. Julius Bauer, Vienna, Austria. Convocation Address.

The scientific program as given above will take about half of the time of the meeting. The remainder of the time will be occupied by clinics. In a general way I will give you our plan of providing clinics. In the afternoon from 1:45 to 4:30, clinics will be held at the Charity Hospital of New Orleans, Touro Infirmary, the Hutchinson Memorial, the Richardson Memorial, Hotel Dieu, the Baptist Hospital, Mercy and

Presbyterian Hospitals. At the Charity Hospital and Touro Infirmary, the program will be changed in the middle of the week, so that two separate programs will be put on at these two hospitals. The same will apply to the program at the Hutchinson Memorial. Clinics will be given at the Charity Hospital by Dr. George Bel, Dr. J. B. Guthrie, Dr. Amadee Granger, Dr. A. E. Fossier, Dr. J. L. Lewis, Dr. Randolph Lyons, Dr. J. H. Musser, Dr. Robert Bernhard, Dr. W. A. Love, Dr. George R. Herrmann, Dr. Philip Jones, and others. At the Charity Hospital, Dr. Julius Bauer, of Vienna, will give a clinic on certain days.

At the Touro Infirmary, clinics will be given by Dr. L. R. DeBuys and his staff and by Dr. I. I. Lemann and his staff. Dr. DeBuys' staff will limit themselves to diseases of children; Dr. Lemann and his staff to internal medicine and to subjects related to internal medicine more or less closely, so that it is quite possible with the present plan to have a surgeon to discuss cases in which the internist and the surgeon come into close contact, such as thyroid cases, abdominal conditions and so on.

At the Baptist Hospital, Dr. Oscar W. Bethea will run the program.

At Hotel Dieu, Dr. S. Chaille Jamison, Dr. Maurice Couret, Dr. L. A. Fortier and others will give clinics.

At the United States Marine Hospital, Dr. W. C. Rucker will be in charge of the program. There are always a large number of interesting tropical and unusual diseases at the Marine Hospital.

At the Hutchinson Memorial, clinics and demonstrations will be given daily. Dr. Wm. M. James and Dr. J. J. Vallarino, of Panama, will demonstrate their preparations and x-ray findings in amebiasis. Dr. J. C. Small, in addition to his scientific paper, will give in more detail than can be done at a large scientific meeting the particulars of the studies he has made in rheumatic fever. Dr. Robert S. Berghoff will give an afternoon demonstration on the diagnosis of chest diseases; Dr. T. J. Perkins, "Constitutional Type in Relation to Mental Disease;" Dr. Aldo Castellani, "Fungus Growth;" Dr. C.



C. Bass, "Malaria;" Dr. F. M. Johns; Dr. H. W. Butler, "A Slide Method for the Diagnosis of Syphilis;" Dr. Roy H. Turner, "Intestinal Microbiology." A clinical pathological conference will be given one or two days.

The program at the Richardson Memorial will be under the supervision of Dr. J. A. Lanford, who has invited Dr. C. W. Duval, Dr. Henry Laurens, Dr. Irving Hardesty and Dr. J. T. Halsey, Professors of Pathology, Physiology, Anatomy and Pharmacology, respectively, with their staffs, to demonstrate research problems that they are actively engaged in or which they recently completed.

#### REDUCED FARES

Twelfth Annual Clinical Session, New Orleans, La.

The Executive Secretary advises that all railroads of the United States and of eastern Canada have granted reduced fares to our Clinical Session on the Certificate Plan of fare and half fare. Those who attend the Session will purchase going ticket at local railroad office and at the same time request a "Certificate." This Certificate, when validated by the proper officers at the registration booth at New Orleans, will entitle attendant to purchase return ticket a half rate.

These reduced rates apply not only to the attendant, but to dependent members of his family.

Going tickets may be purchased from March 1 to 7, and the return ticket may be used up to March 13. For those who desire to remain in New Orleans longer, the return ticket may be used until March 24, upon deposit of Certificate with W. H. Howard, Special Agent located in the City Ticket Office of the Louisville and Nashville Railroad, New Orleans, upon payment of fee of \$1.00 per Certificate receipt at time of deposit.

#### SPECIAL TRAINS

Twelfth Annual Clinical Session, New Orleans, La.

The Southern Railway System, in conjunction with other railroads of the East,

have announced the "Eastern Physicians' Special" train starting from Boston, March 3d, passing through New York, Philadelphia, Baltimore, Washington, to arrive at New Orleans, Monday morning, March 5th. They also announce the "Central States Special," serving eastern Canada and eastern Central States, with connections at Cincinnati and joining the "Eastern Physicians' Special" at Chattanooga and continuing to New Orleans.

Of especial interest is the arrangement for a special train leaving New Orleans after the Convocation on Friday night, March 9th. Heretofore, it often became necessary for many who wished to attend the Convocation to remain over night, because of no suitable train accommodations being available after the Convocation Exercises. This special train has been arranged especially for the convenience of all members who attend the Convocation and wish to leave for the northeastern section of the country immediately thereafter. Time-tables are available in the Executive Secretary's office, and will be distributed to all members residing in the territories served by these special trains.

The route traversed includes the Piedmont Section of Virginia, Blue Ridge Mountain Range, the valleys of the Holston and the Tennessee Rivers, Historical Chattanooga, Industrial Birmingham and across Lake Pontchartrain.

Members residing in the territory served by these trains are requested to make use of them, inasmuch as their comfort and pleasure have been especially arranged for by having them travel together on these trains."

The Executive Offices have on hand a number of old YEAR BOOKS, 1923-24. While these have no present value from the standpoint of directory purposes (the new 1927-28 Year Book was issued during the summer), they may be of interest and historical value to some of our members of more recent election. The Executive Secretary will gladly send a copy to any member upon receipt of 50c in stamps to cover cost of handling and mailing.

# Observations on the Action of Atropin and Calcium and Parathyroid Preparations in Arterial Hypertension\*

By HUGO O. ALTNOW, M.D., *Minneapolis* and JAMES P. O'HARE, M.D., *Boston*

A REVIEW of the titles of articles published within the last five years on the treatment of hypertension suggests the use of twenty-eight inorganic and organic compounds and glandular extracts. If the articles themselves were reviewed, this number would no doubt be doubled and possibly trebled. This condition of affairs carries with it the inference that none of the various preparations suggested has been quite satisfactory.

Our communication deals with three substances: atropin and calcium chloride used in combination, and parathyroid preparations. Before proceeding further, it will not be out of place to state why our selection fell upon these substances, from the large list at our disposal.

We were first stimulated by a communication by Kylin, (1) who reported four cases of hypertension in which a normal blood pressure was obtained after oral administration of atropin and calcium chloride. This report

probably would have attracted no more than passing notice if the use of the drug had been on an entirely empirical basis. Closer examination of the report, however, as well as of other work by the same author, indicated that certain experiments of his and of other investigators to whom he referred, put his work on a suggestive physiological basis. In brief, his conception (1 and 2) is that hypertension is a manifestation of a general nervous disorder and particularly of disordered function or unbalance of the vegetative nervous system. He cites as evidence the variety of symptoms of nervous origin and vaso-motor instability that hypertensive patients complain of: exhaustion, restlessness, insomnia, dizziness, buzzing in the ears, chest oppression, palpitation, tendency to asthma, and others. As further evidence of vaso-motor instability there are the labile blood pressure level and the abnormal or reverse adrenalin reaction (there is a primary drop in blood pressure following intramuscular or intravenous injection of adrenalin). He lays stress on the latter, and according to his interpretation of this phenomenon, it indicates that the parasympa-

\*From the Medical Clinic, Peter Bent Brigham Hospital, Boston.

\*This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

thetic or vagus system has mastery over the sympathetic.

According to his views, the same disordered state that is responsible for hypertension may at other times be the underlying causative factor in asthma, migraine or urticaria.

It must be admitted that his theory of the mechanism of hypertension is difficult for us to follow. His theoretical basis for the use of atropin and calcium in hypertension is stated as follows. (1) Reversed adrenalin reaction shows that the para-sympathetic system has mastery over the sympathetic system and atropin paralyzes the vagus. The aim in giving atropin is to aid in restoring the balance between the para-sympathetic and sympathetic nervous systems. (2) Through the work of Kraus and Zondek it has been demonstrated that calcium ion reduces sympathetic irritability. (3) Investigations of Jensen (3) have demonstrated that calcium content of serum is lowered in hypertension.

The normal fasting serum calcium content, determined by the Kramer-Tisdale method in fifty normal subjects studied by Matz (4) was found to vary between 9 and 12 mg., with an average of 10.28 mg. His normals were adults of all ages and there is no constant relation between lowered serum calcium content and increasing age. Kylin, (1) by using the Ward method, found that in subjects under forty years of age, the minimal and maximal values were .15 mg. and .5 mg. higher than in subjects over forty years of age. Grove and Vines (5) give 10.5 mg., and Sherrill and Copp (6) 9.4 to 10.4 mg., as normal figures. The latter also state that of all the

constituents of the blood, calcium is one of the most constant. Averaging the values quoted, the usual normal serum figure may be arbitrarily set at 10 to 10.5 mg.

We determined the serum calcium by Collip's modification of the Kramer-Tisdale method in fifteen normal adults of all ages, and twelve hypertension cases. Figure I. The normal values were from 9.6 to 11.4 mg., while in hypertension patients, they were 8.6 to 10.6 mg. On seven hypertension patients, the value was 10 mg. or lower. From the curve, it will be noted that the hypertension cases averaged about 1 mg. lower than the normal subjects.

We treated eleven cases of hypertension in the medical wards and the Out-Door Clinic according to the method advocated by Kylin. They all received calcium chloride 1 G. and atropin .00025 G. four times a day for three to four weeks. In six of these cases it had no effect on the blood pressure. In five other cases it might be credited with having some slight effect. We are reproducing two representative curves, Figure II showing no apparent effect following the treatment, and Figure III showing some reduction in blood pressure. In the latter instance we are reproducing one of the best of the five curves. It must be admitted, however, that in some instances the curves obtained from control cases who received no treatment show as good reduction. Figure IV is an example of a control curve of a nervous woman who was under medical observation, during which time she underwent a cystoscopy. In two other cases treated with calcium alone, it appeared to be without effect.

In connection with the administration of calcium, the objection might be raised that an inadequate amount was given. In this connection we cite the work of Matz, (4) who found that 1.3 G. calcium chloride daily produced an average elevation of 2 mg. after it was administered for eleven days.

with nitrogen retention without hypertension, the guanidin secretion by the kidneys is normal. Major and Stephenson (8) also found that dimethylguanidin had the most marked pressor effect. By injecting calcium chloride alone or in combination with potassium chloride, the pressor effect could be

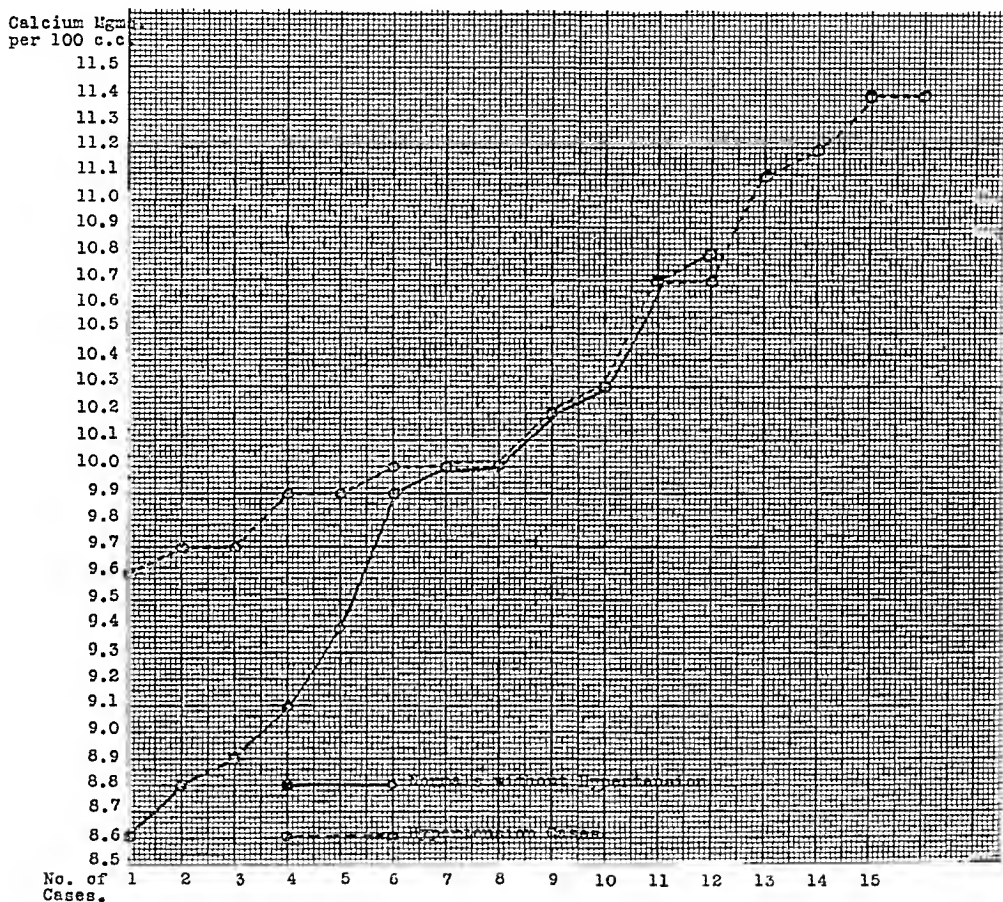


FIG. 1

During the time that we were using the atropin and calcium, Major and Stephenson (7 and 8) demonstrated the prolonged pressor effect of methylguanidin when injected intravenously in dogs. Major (9) also states that guanidin retention occurs on the part of the kidneys in patients with hypertension and chronic nephritis with hypertension, but with chronic nephritis

neutralized, or if injected before methylguanidin, the pressor effect of this substance could be abolished. They conclude that these results suggest that calcium chloride and potassium chloride exert a definite effect on dimethylguanidin.

This work incited in us an interest in methylguanidin, and in our review of the literature, it came to our

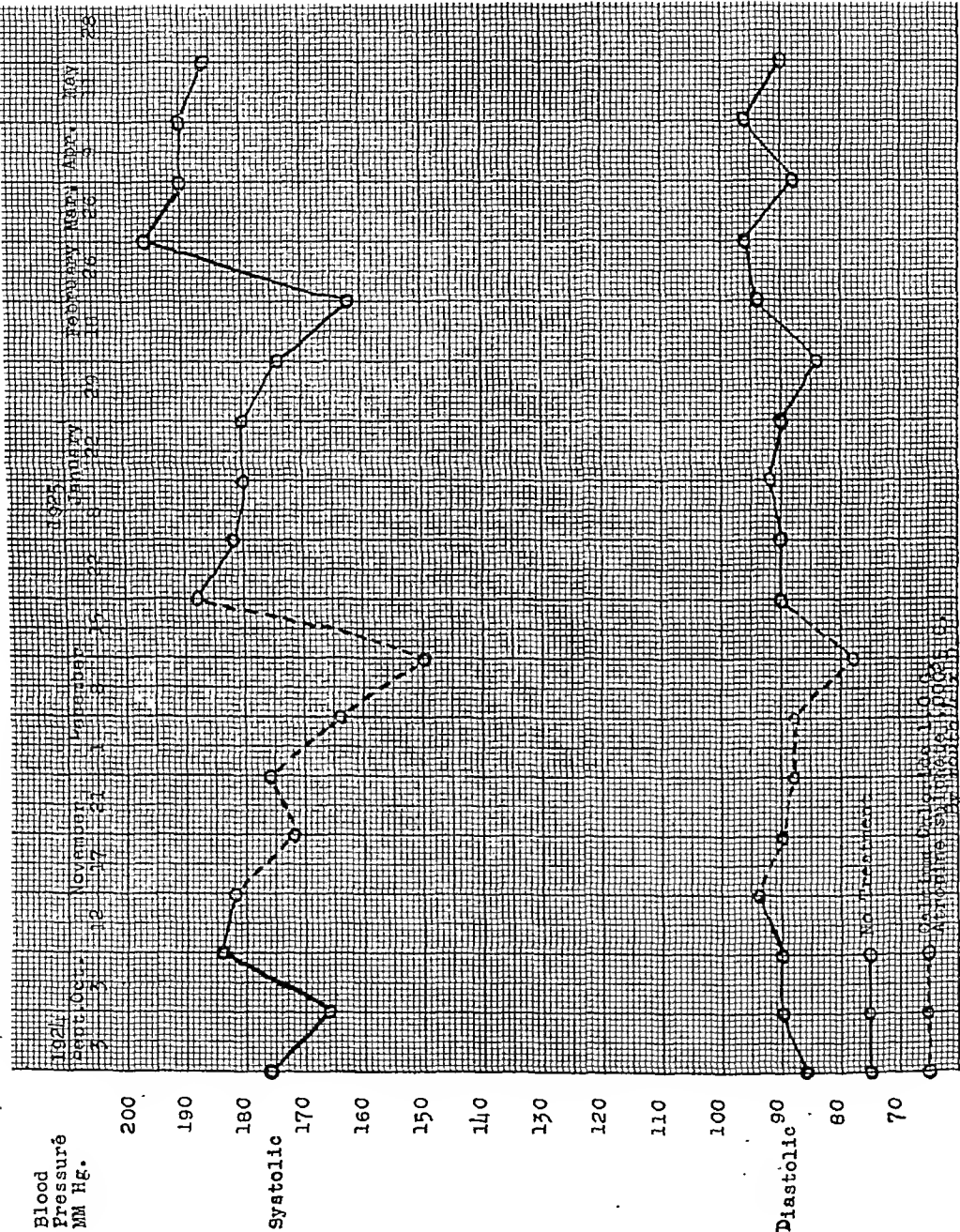


FIG. 2

notice that Paton (10) had made some observations suggesting that tetany thyreopriva might be due to intoxication by guanidin bases. Further, Vines, (11) who has done some research on the parathyroid gland, assigns a dual

izing the information obtained from these sources it was easy to construct an interesting theory of hypertension that implicated the parathyroid gland. In order to test the soundness of this theory, we decided to make use of

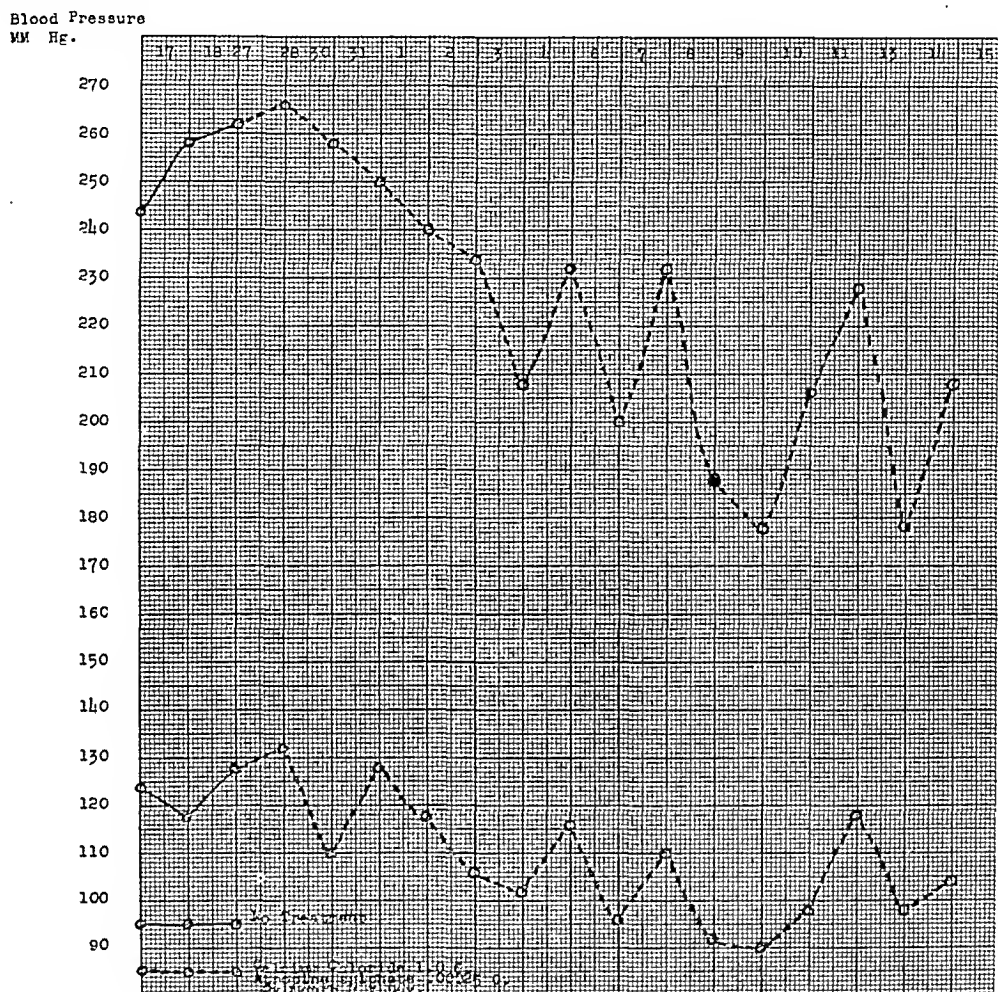


FIG. 3

function to this gland: (1) the removal of certain toxic substances, either guanidin or its methyl compounds, from the blood, and (2) regulation of the calcium metabolism. In a personal communication to Hanson (12) he expressed the opinion that the former action was probably due to an enzyme and the latter to a hormone. By util-

parathyroid preparations in some cases of hypertension. From work published by Major, (9) it is known to us that the same relationship of the parathyroid to hypertension received consideration by him. He reports ten control experiments in which he used Hanson's parathyroid preparation intravenously in five dogs and Collip's in



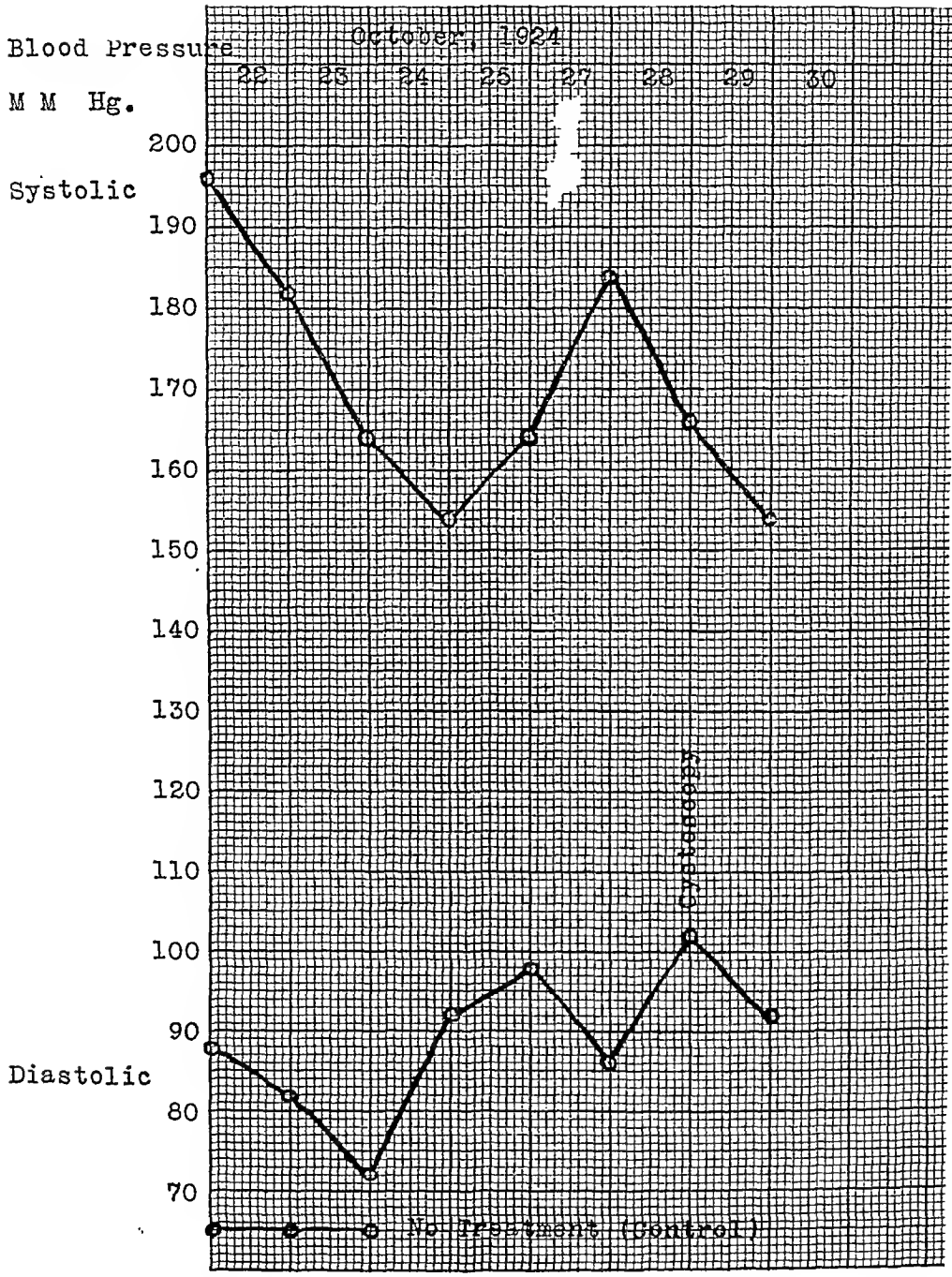


FIG. 4

five others. It was found to have no effect on normal blood pressure, but when the experiments were repeated in animals with blood pressure raised by injection with methylguanidin, a prompt fall in blood pressure was produced with both preparations. These results are of interest to us, since the parathyroid preparation that we used in our observations for intramuscular injection was obtained from Hanson.

In our observation of parathyroid administration in clinical hypertension, we used Parathyroid Extract .0065 G. (Lilly) four times a day orally and a solution (Hanson's Hydrochloric X Sicca) for intramuscular administration.

Vines (11) states that the maximum parathyroid effect by the oral administration of extract 1/10 grain (.0065 G.) is obtained in about eight days. We believe that this preparation has been effective clinically in chronic tetany and in other clinical states where it was desired to maintain normal blood calcium levels.

We were supplied with parathyroid for intramuscular injection through the kindness of Dr. A. M. Hanson. The method of preparation of this substance is described by him. (13) The potency of the preparation in raising the serum calcium in parathyroidectomized dogs is also demonstrated. (14) Hanson removed the parathyroid in four dogs, on which a previous normal serum calcium determination had been made, namely, 11 to 12 mg. The day after operation, a drop in serum calcium of 2 to 3 mg. took place. By two 5 c.c. intramuscular injections on the second and third days, the maximum rise obtained was 15.7 to

20 mg., 64 to 72 hours after the first injection.

Hanson claims for his preparation (15) that it detoxicates guanidin and that it raises the ionic calcium to normal. He suggests its use in varicose ulcer, chronic infections, dental caries and tetany. In his published writings he has not, to our knowledge, advocated its use in hypertension. We advised him of our intended use of his preparation and are indebted to him for suggestions as to dosage and frequency of administration.

We used parathyroid extract .0065 gm. by mouth in three cases of hypertension over a sufficiently long period to obtain its action, without any apparent effect on the blood pressure. Hanson's Parathyroid Extract HCL X Sicca was used in three cases in increasing daily dosage until a maximum of .039 gm. was given, and this dosage was then maintained. Observations on the immediate and sustained effect on the blood pressure were made. For immediate effect, the blood pressure estimations were made before 3 minutes, and 30 minutes and one hour after injection. No constant immediate effect from the parathyroid was discernible. The small variations that occurred were within normal limits of blood pressure variation. In two of the three cases there did not appear to be any sustained depressor effect on the blood pressure. One record (Figure V) is reproduced, together with that of the third patient, (Figure VI) in which there appeared for a time to be a decline in blood pressure, but there followed a rather abrupt rise, while the patient was still receiving parathyroid.



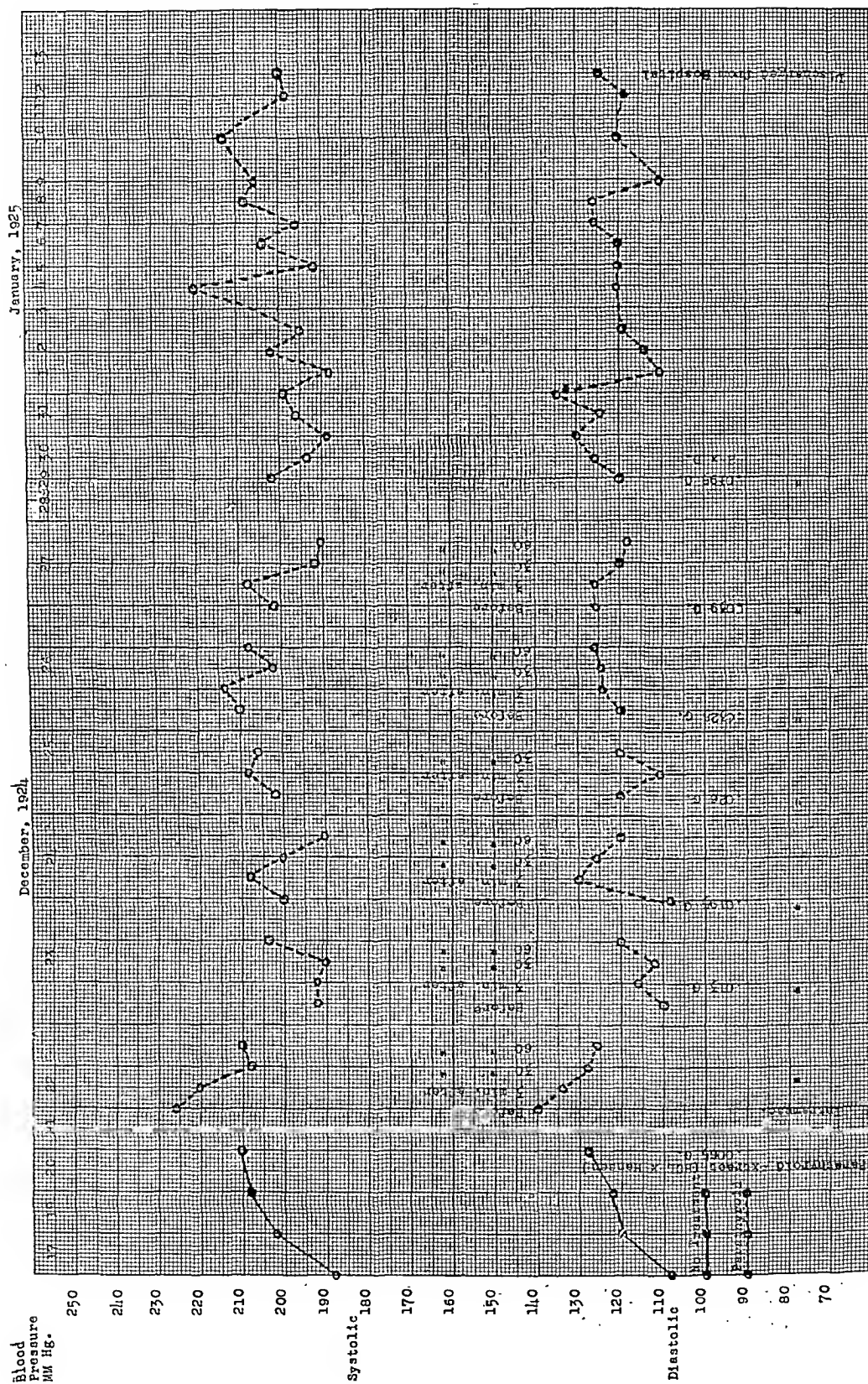


FIG. 5

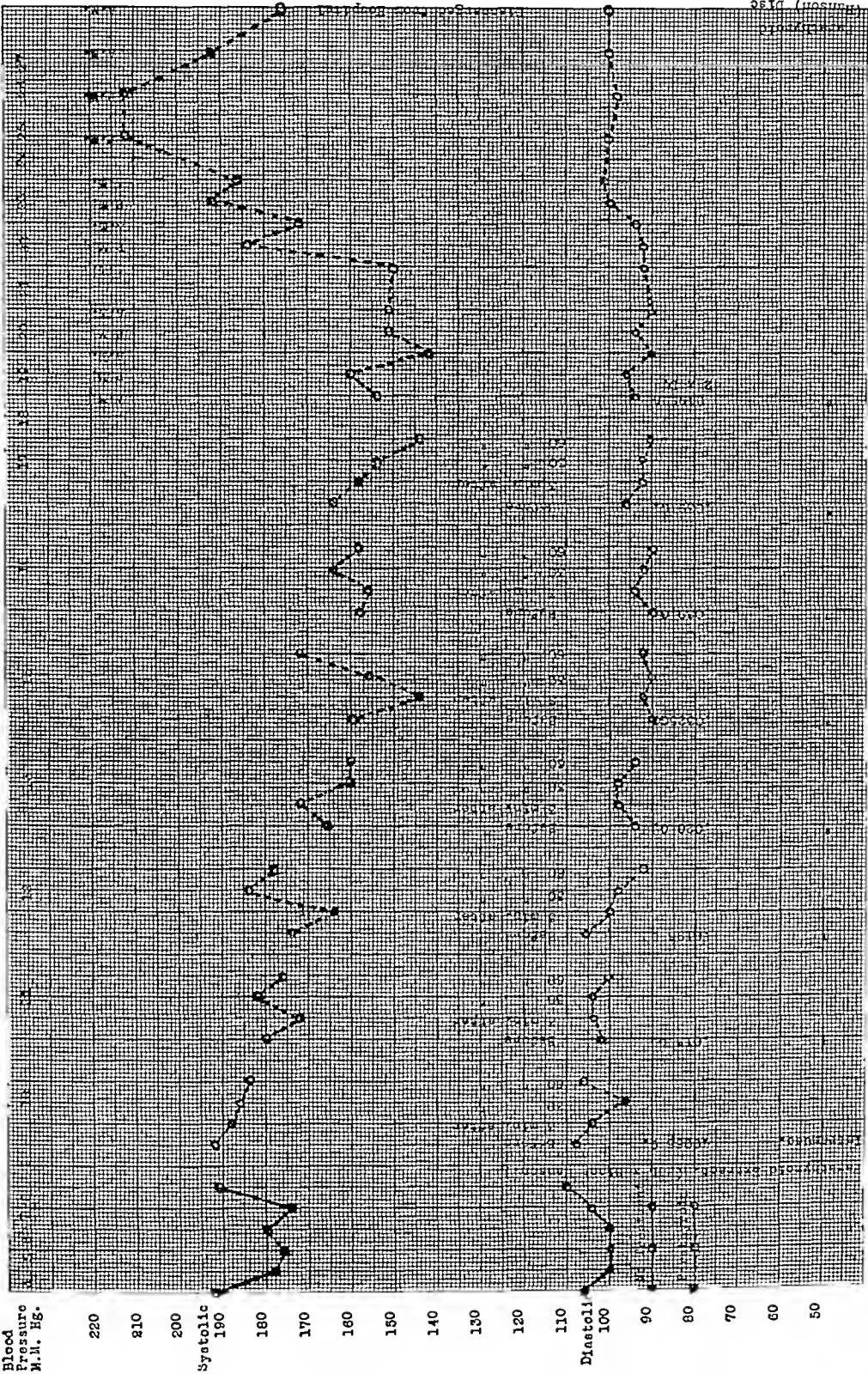


FIG. 6

We realize that it is not permissible to draw conclusions from the results obtained on the patients we had under treatment without a check on serum calcium. However, we gave both the calcium and parathyroid preparations in what are generally considered to be adequate dosages.

Our observations indicate to us that

the problem of hypertension is still a more complex one than can be explained on the basis of a disordered calcium and guanidin metabolism. There apparently are other factors operative in its production, our knowledge of which at the present time is inadequate to explain its mechanism and manifestations.

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# The Pathological and Clinical Significance of Congenital One-Sided Kidney Defect, With the Presentation of Three New Cases of Agenesis and One of Aplasia\*

BY CARL H. FORTUNE, M.D., *Senior Instructor in Pathology in The University of Michigan*

CONGENITAL one-sided kidney defect has been reported by many writers, beginning with Aristotle, because it has been considered a rare and interesting structural anomaly. Little attention was paid by the older writers to the clinical significance, probably partly because they considered the condition extremely unusual, and partly because many of the cases occurred in old people dying of other causes. The earlier reports, as well as some of the recent ones, are merely anatomical descriptions, without clinical data or description of other pathology found post-mortem. In the latter part of the nineteenth century with the development of surgery of the kidney, a number of instances of operative removal of a patient's only kidney, with the inevitable fatal result, attracted attention to that particular phase of the subject. Still more recently there has been some discussion of the possibility that such a malformation might render the individual more susceptible to kidney disease of various

sorts and be a factor in influencing the prognosis in cases of pathology of the urinary tract. Four cases have occurred in the autopsy service of the University of Michigan which illustrate the types of cases found in the rather abundant literature which has accumulated on the subject. It is the purpose of this paper to present these cases together with the data gathered from a study of the recorded cases, which bears on the clinical importance of this condition, and to discuss the anatomical findings in such cases.

Obviously not all cases in which there is only one functioning kidney are analogous, either structurally or embryologically, and a grouping of cases is essential to any orderly discussion. One of the earliest is that of Rokitansky, (1) which, though it introduced terms which may be confusing, has influenced strongly all later classifications and has formed the basis for the naming of most recorded cases. He stated the situation as follows:

"When one kidney only is present, it is important to distinguish between the unsymmetrical and the solitary kidney. The former is represented by a

\*From the Pathological Laboratory of the University of Michigan.

right or left kidney, which is normal in regard to position and conformation, and occasionally rather enlarged, its fellow being deficient. The solitary kidney is the result of a fusion of the two organs, and therefore offers the characters peculiar to this arrangement in a greater or less degree. The lowest degree of fusion is seen in the horseshoe kidney (*ren unguiformis*); the two kidneys are united at their inferior portions by a flat riband-like or rounded bridge of tissue, which crosses the vertebral column. In the higher degrees the two lateral portions approach one another more and more, until they reach the highest degree, in which a single disk-like kidney, lying in the median line and provided with a double or single calyx, represents complete fusion."

For purposes of more accurate placing and elimination two other classes may well be introduced, giving four groups, as follows:

Class I. True one-sided congenital defect or agenesis, the "unsymmetrical kidney" of Rokitansky. By this it is understood that there is no tissue present on one side which can be grossly or microscopically recognized as kidney parenchyma.

Class II. Aplasia of one kidney. This group includes those cases in which atypical kidney parenchyma is present on one side on microscopic examination, but in which the development is so rudimentary that there is no functional kidney tissue.

Class III. Hypoplasia of one kidney, in which one kidney is much smaller than its fellow, but still exists as a functioning kidney.

Class IV. Various forms of fusion, the "solitary kidney" of Rokitansky.

Class V. Marked secondary atrophy or destruction of one kidney, not a disturbance of development.

Cases have often been listed without thorough study and classification, so that it is difficult to state definitely in which group a given case should be placed, and from a clinical point of view it often makes little difference whether a kidney is congenitally absent or destroyed by some secondary process. Of the four cases presented here three seem to fall in the first class, while the fourth might be properly placed in class two. Hence we shall be concerned only with agenesis and aplasia of one kidney, and in surveying the literature an effort has been made to exclude all those cases which represented a fusion or secondary atrophy, as well as those of hypoplasia. I have also endeavored to draw a distinction between the true agenesis and aplasia of one kidney, using the same criteria as will be pointed out in the discussion of the following cases.

#### Case I. *Aplasia of left kidney.*

A. B., age 5 months, male was admitted to the surgery service of the University Hospital January 14, 1917 for correction of a double hare lip and cleft palate. Preliminary wiring operations were performed on January 17 and on January 31. Early in March the child developed a severe diarrhoea and was transferred to the pediatrics service for treatment on March 19. The diarrhoea continued with much blood and mucus, the fluid output being apparently greater than the fluid intake. The child became very dehydrated and died on March 18, 1917. At no time during his stay in the hospital were there any symptoms indicating renal disturbance or insufficiency, and the case record



contains no note of anything in the child's past history pointing toward disturbance of kidney function.

- Autopsy-96-U. Prosector: Dr. Weller.

The body is that of a poorly nourished male child showing to external examination bilateral cheilognathopalatoschisis, for which a preliminary plastic operation had been performed. The left pinna shows almost complete absence, and the right pinna shows a

Both adrenals were found in the normal location and appeared to be normal in structure.

The right kidney is large, measuring 7x4x2½ cm. The ureter is normal. On the left side is a soft flattened mass, lying in the usual location of the kidney, measuring 24x17x3 millimeters. This communicates with the bladder by a tubular structure having the appearance of a rudimentary ureter.

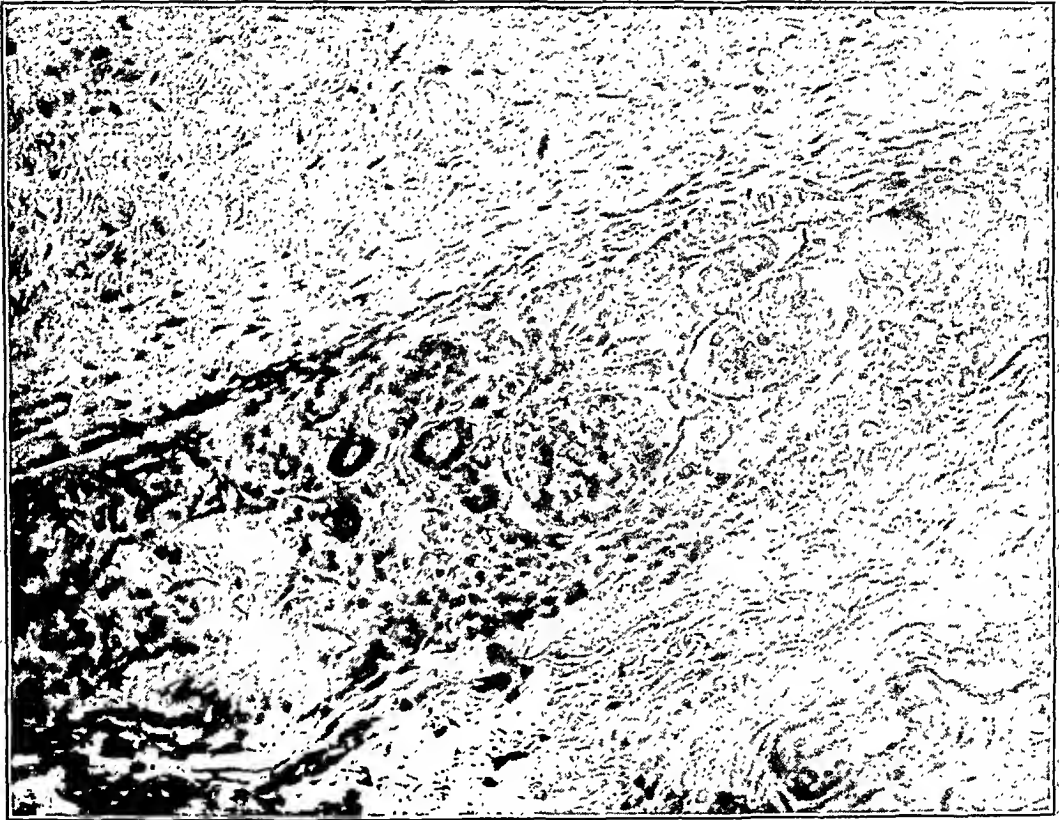


FIGURE 1. Photomicrograph of the aplastic kidney from Case I. There are a few glomeruli and tubules in a mass of dense fibrous tissue. Some of the glomeruli show obliteration. Haemalum and eosin stain, Zeiss AA ocular with number 4 compensating ocular.

similar condition in less marked degree. Both testes were in the scrotum. There is a small umbilical hernia.

On examination of the viscera the only anomalies outside of the genito-urinary tract were the occurrence of a Meckel's diverticulum measuring 9 cm. in length, located 60 cm. above the ileo-caecal valve, multiple diverticula of the colon, and a stenosis of the aorta at the isthmus.

There are no anomalies of the genital apparatus.

Microscopic examination of the kidneys: Dr. Warthin.

*Right kidney:* Numerous concretions of lime salts in the straight tubules, loops of Henle, and distal convoluted tubules. The convoluted tubules show hypertrophy. The nephrogenic zone is increased. Active new

formation of kidney tissue. Hyaline casts in many collecting tubules.

*Left kidney:* Is represented by a mass of hyaline connective tissue surrounding a cleft lined by flattened epithelium. At one pole there is a little group of glomeruli showing stages of obliteration and a few tubules.

#### Pathological Diagnosis:

Multiple anomalies. Bilateral cheilognathopalatoschisis. Meckel's diverticulum. Multiple diverticula of colon. Malformations of ear. Stenosis of aortic isthmus. *Aplasia of left kidney. Hypertrophy of right kidney with acute nephritis.* "Chalk infarcts." Renal insufficiency. Lymphoid exhaustion. Hypoplasia of adrenal medulla. General passive congestion.

This case represents a high degree of aplasia and no doubt many of the recorded cases in the literature of congenital absence of the kidney with the presence of the corresponding ureter and no microscopic examination of the tissue around the ureter must belong in this group. However, with the presence of tubules and glomeruli, no matter how rudimentary, this must be classed as an aplasia rather than an agenesis. A photomicrograph of this kidney is shown in figure 1.

Case II. *Agenesis of right kidney with persistence of right ureter. Associated genital malformations.*

Mrs. A. E., age 68, was admitted to the University Hospital May 21, 1926, as an emergency, after being struck by an automobile. A fracture of the skull was demonstrated by X-ray, but since there was no evidence of pressure and since the fracture was not compound no operative procedures were undertaken. The patient was unconscious for some days, and during the period following her recovery of consciousness she was irrational at times. During the routine physical examination a carcinoma of the left breast was discovered. Otherwise there were no findings of importance.

During her stay in the hospital the patient developed a toxic erythema for which no cause was demonstrated. On July 3 there was a sharp rise in temperature and the patient became comatose, dying on July 5, 1926.

No clinical findings are noted pointing toward an impairment of kidney function. A catheterized specimen of urine was negative except for the occurrence of 300-400 white blood cells per low power field of the microscope.

Autopsy 3-AE. Prosector: Dr. Fortune. Gross description of the genito-urinary system.

The right and left adrenals were found in their normal locations. The adrenal arteries and veins on the two sides were isolated and found to be without abnormality. The adrenals are of usual size, the cortex showing lipoidosis, but otherwise they are negative to gross inspection.

The left kidney was found in its normal location. Its vessels were dissected out and found to be normal. There is slight hypertrophy of this kidney, the measurements being 12x6x6 cm., and the weight, with some of the fatty capsule which was very adherent, was 210 grams. There is a very abundant fatty capsule which was removed with difficulty. The fibrous capsule stripped with ease leaving a smooth surface, showing a slight suggestion of foetal lobulation. Section showed a normal relation between cortex and medulla. The pelvis is of normal size and shape, and shows no evidence of inflammation. The ureter is of normal size and patent throughout. The ureteral orifice in the bladder is normally located in respect to the trigone.

At the corresponding level on the right no kidney could be found. No renal artery is given off from the aorta and no renal veins could be demonstrated. Nothing could be found in the usual location representing ureter, and there is no ureteral orifice in the bladder on the right side and the right half of the trigone is undeveloped.

There is a tubular structure terminating on the right side of the vagina about 5 mm. below the cervix uteri and arising in a tapering end 11 cm. higher at about the level of the brim of the lesser pelvis. This tube has

an external diameter at its lower end about equal to that of a lead pencil and its wall is about 2 mm. in thickness. It arises and ends blindly. Pieces were taken for microscopic study from the tapering end and from lower down.

The body of the uterus is distinctly divided into two cornua. The lesser of these is on the right and measures 3 cm. in length. The left horn is 4 cm. in length. The Fallopian tubes arise from the extremities of these cornua and show no thickening or dilatation. They both show an equal degree of development. The ovaries are of equal size. Both are wrinkled, firm and pale in color.

The peritoneum reflected from the right horn of the uterus forms a transverse band extending back to the rectum and roofs over about half of the pouch of Douglas.

The vagina shows no septum. The walls are smooth, rugae are not well marked. The cervix uteri is patulous and the little finger is readily passed in to the point of bifurcation of the body. No septum is present.

An anomalous artery arises from the anterior surface of the aorta 4 cm. above the bifurcation and distributes over the posterior surface of the rectum.

Microscopic examination of kidney, adrenals and anomalous tubular structure to right of vagina: Dr. Weller.

*Adrenals:* Of about normal size. Moderate patchy lipoidosis. Numerous small foci of mononuclear infiltration in the cortical portion. One adrenal shows accessory adrenal cortical tissue outside the capsule. This occurs in two forms: as spherical encapsulated nodules such as are usually seen, and as a diffuse intermingling of adrenal cortical cells with periadrenal fat.

*Left Kidney:* Moderate hypertrophy. Many large glomeruli. Numerous foci of active inflammation, chiefly near the capsule, and practically always centering about a scarred glomerulus. In some of the loops of Henle and straight tubules there is a deposit of a brown granular substance,—hemosiderin.

*Anomalous Tubular Structure to the Right of Uterus and Vagina:* This is a dilated tubular structure having a muscular wall. The musculature is not definitely arranged

in layers, much of it running obliquely, although this differs in different levels. In one portion there is a well defined inner circular layer and obliquely running outer layer. The epithelium is of a transitional type, showing 2 or 3 layers of somewhat irregular columnar cells capped by larger flattened cells. The dilated lumen contains a mass of pink-staining albuminous material containing desquamated epithelial cells. Through this mass there are peculiar oval and cylindrical bluish staining bodies, probably older epithelial hyaline. In the muscular wall there are glandular structures in which these hyaline masses appear to form. These gland-like structures have epithelium somewhat like the main lumen and may be diverticula from it.

#### Pathological Diagnosis:

Fracture of skull in left occipito-temporal region. "Traumatic hemorrhagic encephalitis." Marked aortic and coronary atherosclerosis. Partial coronary occlusion. Myocardial fibrosis. Subepicardial fatty infiltration. Subendocardial fatty degenerative infiltration. Advanced scirrhous adenocarcinoma of left breast with metastasis to axillary lymph nodes. Chronic catarrhal bronchitis with acute purulent exacerbation. Chronic atrophic catarrhal gastro-enterocolitis. Old tuberculosis of bronchial nodes. Chronic purulent cholecystitis. Localized chronic parenchymatous hepatitis. Chronic hypertrophic purulent cystitis. *Multiple anomalies of genito-urinary tract (agenesia of right kidney and upper segment of right ureter, malposition of lower right ureter, bicornuate uterus with hypoplasia of right cornua, heterotopia of adrenal cortex in periadrenal adipose tissue).* Moderate compensatory hypertrophy of left kidney with scattered foci of chronic inflammation. Adenomatous colloid goiter. Fatty atrophy of pancreas. Lipoidosis of adrenals. Congestion, oedema, and parenchymatous degeneration of all organs.

The condition as regards the kidney in this case differs from the preceding only in the absence of the tubules and glomeruli. The question may well arise whether the gland-like structures found



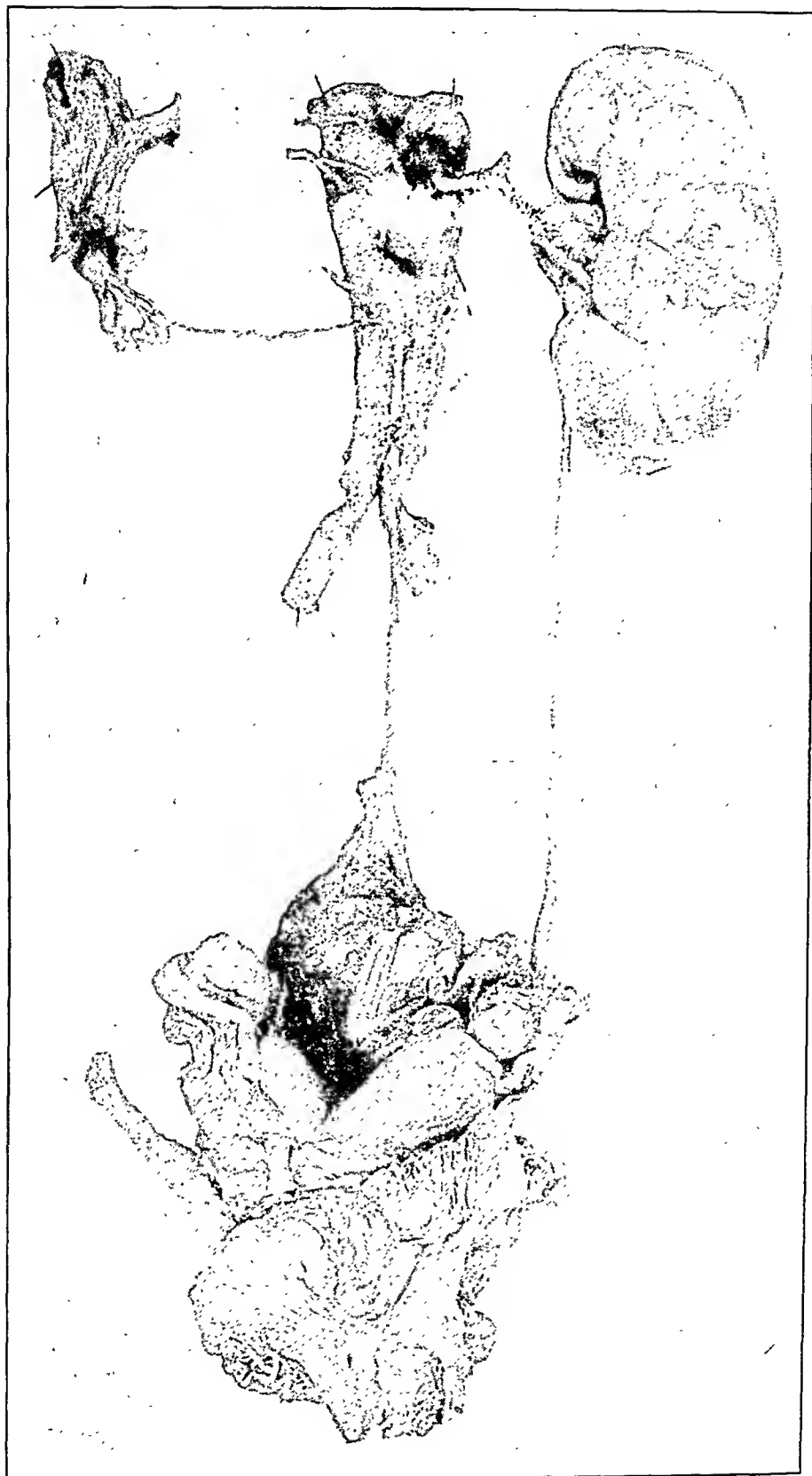


FIG. 2. Gross preparation of the genito-urinary tract from Case II. The right kidney and vessels and the right ureteral orifice in the bladder are absent. A rudimentary ureter is seen arising to the right of the vagina. The bicornuate uterus shows a poorly developed right horn.

around the ureter-like tube are kidney tubules and whether this should not be classed as a case of rudimentary kidney. However, the microscopic appearance of the epithelium indicates that they should be considered as a part of the ureter, perhaps as rudimentary calices, and hence this case was classed as a true agenesis. Certain writers, notably Aschoff (2) state that in agenesis of the kidney the ureter is always absent and would include all such cases as this as aplasia of the kidney. Since the ureter and kidney are not inseparably linked embryologically, as will be pointed out later, there seems no reason why the ureter cannot exist without the kidney and most of those who have written on this subject are willing to admit such a possibility. These cases serve to show how readily one condition grades over into the next more severe and how difficult a classification may sometimes become. The associated genital malformations in this case are very interesting and also quite common findings. Their occurrence and significance will be discussed more fully later. A photograph of the intact urogenital system is shown in figure 2, while figure 3 is a photomicrograph of the rudimentary ureter.

Case III. *Agenesis of left kidney, ureter and adrenal. Associated genital malformations.*

I. C., female, age 15, was seen in the outpatient department of the University Hospital April 11, 1923 on refer from a school physician with question of thyroid disturbance. A diagnosis of simple colloid goiter was made and there is nothing in the case record to indicate that she presented any evidence of disturbance of kidney function. She was admitted to the hospital at 4 p. m. on September 18, 1923 in a stuporous condi-

tion. Her father stated that she had been well until three days previous, when she scratched a boil on the right cheek. On physical examination a crusted area was found in the middle of the right cheek. The whole right side of the face and neck was swollen and reddened. The skin of the entire body was ashen except for cyanosis over the extremities. The pulse was irregular and rapid. Breathing was shallow and rapid. There were no signs of meningitis. She died at 8 p. m. on the day of admission. The only laboratory examination made was a blood culture, which was positive for streptococcus hemolyticus.

Autopsy 39-AB. Prosector, Dr. Hall.

Gross description of the genito-urinary system: Examination of the location normally occupied by the left adrenal showed no tissue suggestive of adrenal. The right adrenal is of normal size and shape and in the normal location.

In the usual position of the left kidney there is only a mass of fat, which on microscopic examination showed no trace of kidney structure. The left ureter is also totally absent.

The right kidney is slightly larger than normal, measuring  $15 \times 6\frac{1}{2} \times 3\frac{1}{2}$  cm. The fatty capsule is fairly abundant and stripped readily. The fibrous capsule stripped readily, leaving a surface smooth, except for foetal lobulation. The right ureter is of usual size and shows no variations from normal.

The uterus is unicornuate in type. The right horn is well developed and attached to this is a tube and ovary of normal appearance. The left horn shows no development whatever and the left tube which is rudimentary is attached to the wall of the pelvis by a rudimentary broad ligament and neither tube nor ligament have any connection with the body of the uterus. In connection with this rudimentary tube is a small ovary, described as being the size of a large bean, but with a hemorrhagic cystic Graafian follicle the size of an olive arising from it. The hymen is unruptured and normal in appearance. The vagina is of a normal virginal type and shows no septum.

Microscopic Examination *Right Kidney:* Dr. Warthin.

Passive congestion and slight cloudy swelling. Metastatic abscesses with central colonies of cocci plugging the vessels. Excretory abscesses in the pyramids. No evidence of hypertrophy in the microscopic section.

*left ovary, tube and broad ligament. Unicornuate uterus. Thymico-lymphatic constitution.*

This case represents one of the most complete defects of the urinary tract seen in the female. The similarity of



FIGURE 3. Photomicrograph of the upper segment of the rudimentary ureter from Case II. The tube is lined by an epithelium of a transitional type, and its lumen contains a mass of pink staining albuminous material. In the muscular wall is seen a gland-like structure lined by epithelium of the same type as in the main lumen. Haemalum and eosin stain, Zeiss AA objective without ocular.

#### Pathological Diagnosis:

Septico-pyemia. Multiple pyemic abscesses in thyroid, heart muscle, lungs, kidneys, and liver. Diffuse phlegmon of the right side of the face, right orbit and upper portion of the right side of the neck, following a furuncle on the right cheek. Acute passive congestion and parenchymatous degeneration of all organs. *Anomalous development of left urogenital tract. Agenesis of left kidney, ureter and adrenal. Aplasia of*

the genital anomalies to those of the preceding case will be noted, but as the urinary defect has become more complete, the lack of development of the genitals on the corresponding side has become more pronounced. The absence of the adrenal is, as might be expected, a rather common finding in such cases.

Case IV. *Agnesia of left kidney and ureter. Associated genital malformations. Heterotopia of right adrenal in kidney.*

G. M., age 21, single, entered the University Hospital December 9, 1926 with the chief complaint of impairment of vision for six weeks. Three years previous to his admission he was examined and passed for life insurance. A year and a half later he was again examined for life insurance, but at this time the systolic blood pressure was 230 and albumin was found in the urine. He gave a doubtful history of a discharging ear in infancy, boils on the neck three years, and a pharyngeal abscess two years before admission. He had noticed no edema, dizziness, or headache, but he did complain of shortness of breath and failing appetite, also a loss in weight of 15 pounds in one year.

Physical examination showed marked enlargement of the heart, the cardiac apex extending 13 cm. to the left of the midsternal line. There was a pericardial friction rub near the apex. Visible pulsation of the carotid arteries was noted. The blood pressure was 240/140. The optic fundi showed the characteristic changes of chronic nephritis. There was no edema or ascites noted.

Laboratory tests showed the urine to be acid with a sp. g. 1.010, albumin 4 plus, and a few finely granular casts. On December 10 there was no elimination of phenol-sulphone-phthalein in two hours. The non-protein nitrogen of the blood rose from 84.5 mgs. per 100 c.c. on admission to 210 mgs. per 100 c.c. four days later. A concentration test gave a variation in the specific gravity of the urine from 1.010 to 1.013.

On December 13 pleural friction rubs and râles in the lung bases were heard. The patient became stuporous and died on December 14, 1926.

The clinical diagnosis was chronic nephritis, hypertensive heart disease, lobar pneumonia, and cardiac failure.

Autopsy 129-AE. Prosector: Dr. Fortune.  
Gross description of genito-urinary system.

The abdominal aorta, inferior vena cava, adrenals, right kidney and pelvic organs were removed en masse.

Upon dissecting away the adipose tissue the right adrenal is found in its normal location. It is of normal size but very much flattened having the contour of a slightly irregular disc. It receives its blood supply from an artery arising from the aorta just lateral to the superior mesenteric artery and is drained by a vein emptying into the vena cava just opposite to the renal vein of the opposite side. These vessels are surrounded by sympathetic ganglia of the coeliac group, and hemolymph nodes.

No kidney can be found on the left side nor anything suggestive of kidney anlage. No artery arises from the aorta to correspond to the left renal artery and no vein empties into the vena cava to represent the left renal vein. A small artery arises from the aorta just below the left adrenal artery and terminates in the mass of sympathetic ganglia and hemolymph nodes. Microscopic sections of this area showed nothing suggestive of kidney tissue.

No ureter, nor anything suggestive of rudimentary ureter, could be found on the left side and the bladder contains no ureteral orifice on the left side. The left half of the trigone is undeveloped.

The right adrenal was found in its normal location. It is also markedly flattened and has the form of an oval plaque, slightly larger than that on the left. It receives its blood partly by an artery from the aorta distributing to it alone and partly from another artery distributing partly to it and partly to the superior pole of the right kidney. It is drained by a vein emptying into the inferior vena cava. The adrenal is very closely joined to the kidney and grossly there appears to be at least a fusion of the two capsules, if not an actual heterotopia of adrenal into kidney substance.

The right kidney averages 11 x 6 x 4 cm. The capsule stripped with great difficulty showing a tendency to splitting. The surface left is very granular, the granules averaging about 2 mm. in diameter. On section, the kidney cortex is found to average 5 mm. in thickness. The pelvis is dilated and moderate congestion of the mucosa is present. The kidney parenchyma appears swollen with

decreased translucency—a picture suggesting cloudy swelling. The whole is indicative of a marked secondary contraction of a previously hypertrophic kidney. The right ureter is dilated, averaging 1 cm. in external diameter. It opens into the bladder by a normally located ureteral orifice.

The right seminal vesicle was found in its normal location. It is of usual size. On section, it was found to contain a turbid fluid resembling semen. The right vas is in normal location. It is not thickened, and in no way appears abnormal.

On the left side no seminal vesicle or vas deferens could be located, although the bladder was dissected entirely from the rectum. The prostate is small and firm. It is slightly asymmetrical, there being a pea sized accessory lobe in about the usual location of the left seminal vesicle. No unusual appearance was found on section. The ejaculatory duct on the right side is normal in appearance. No ejaculatory duct could be located on the left.

The right testis is of normal size. On section, there is the usual granular appearance of the body. The epididymis arises at the usual location. It is of normal size, shows no evidence of pathology. The right vas arises at the normal location.

The left testis is of about the same size as the right. On section, the parenchyma is slightly less granular than on the right, but there is no marked gross difference. The epididymis arises at its usual location by seven vasa efferentia. The epididymis is, however, only seven centimeters in total length and becomes rapidly smaller toward the end. It terminates in a fibrous strand which attaches alongside the vasa efferentia as they arise from the mediastinum testis. No vas deferens arises from the epididymis.

Microscopic findings bearing on the renal condition: Dr. Warthin:

*Heart:* Advanced coronary atherosclerosis. Hypertrophy of heart muscle with secondary atrophy and diffuse fatty degenerative infiltration. Marked increase in stroma throughout the heart. Patches of sclerosis are present in the left ventricular wall. Endocardium shows sclerosis. Marked subepi-

cardial fatty infiltration with serous atrophy.

*Aorta:* Well advanced atherosclerosis.

*Right Kidney:* Late stage of chronic glomerulo-tubular nephritis. Advanced contraction. Right adrenal shows heterotopia into kidney cortex beneath the capsule. There is marked sclerosis of the renal vessels, secondary to hypertrophy. Some vessels show obliterating endarteritis.

*Both testes:* Aspermatogenesis. Congestion and oedema.

#### Pathological Diagnosis:

*Agnesia of left kidney and ureter, left seminal vesicle and vas. Advanced glomerulo-tubular nephritis of right with marked contraction. Heterotopia of right adrenal into kidney cortex. Right-sided hydroureter and chronic pyelitis. Cardiac hypertrophy and dilatation. Cardiac insufficiency. Brown induration of lungs with marked edema, congestion and emphysema. Wet brain and meninges. Hydrothorax, hydropericardium and ascites. Advanced atherosclerosis of renal and coronary arteries and aorta. Fatty infiltration of heart and liver. Colloid goiter. Colloid cyst in pituitary. Atrophy, passive congestion and parenchymatous degeneration of all organs. Chronic stasis catarrh of gastro-intestinal tract. Lipoidosis of adrenals.*

The anatomical features of this case correspond very closely to those of the preceding case except for the sex difference and the presence of the adrenal in case IV. It is difficult to state just what, if any, significance should be attached to the heterotopia of the right adrenal in the kidney substance. Very few instances are reported in connection with absence of the other kidney. The significance of heterotopia of the adrenal in kidney and liver has been discussed by Weller (3) and he concludes that the condition is usually found in cases of constitutional pathol-

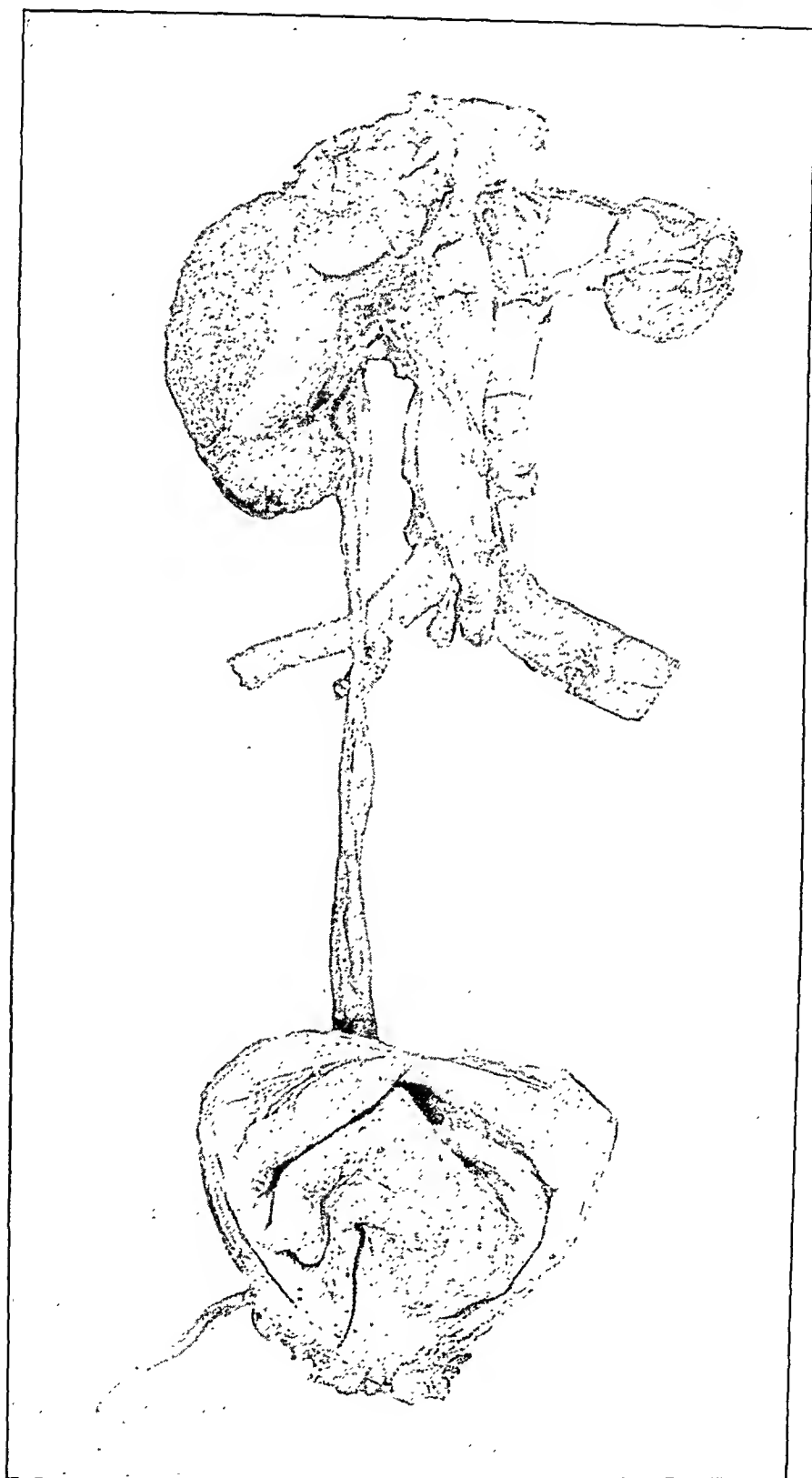


FIGURE 4. Gross preparation of the genito-urinary tract from Case IV. Both adrenals are present. The left kidney, renal vessels, ureter, seminal vesicle, vas deferens and a portion of the epididymis are absent. There is only one ureteral orifice in the bladder. The right kidney shows marked secondary contraction.

ogy and there is no especial connection between it and malformations of the genito-urinary tract. Its occurrence in this case probably has no significance other than that we are dealing with a constitutionally pathologic individual. The significance of the genital malformations will be discussed later. Figure 4 is a photograph of the intact urogenital system from this case and figure 5 shows the malformation of the epididymis.

*Evidence as to side most frequently involved:*

The available recorded cases of congenital one-sided kidney defect have been studied and of these 422, including the three listed above, were considered to be true agenesis of the kidney while two recorded as congenital absence of one kidney seemed definitely to fall in the class of aplasias. Only those cases were included where autopsies had been performed. Several cases reported as rudimentary kidney were excluded on the ground that from the description it appeared that the case was one of a hypoplastic but functional kidney. It is probable that in many of the reported cases; if careful microscopic examination had been made of the tissue in the region normally occupied by the kidney, the group of aplastic kidneys would have been increased at the expense of the group of true agenesis, but unfortunately in many of the cases such evidence is lacking. Of these cases the side of the kidney defect was noted in 387 cases, in 218 of which it was the left and in 179 the right. This proportion agrees in a general way with that found by other writers, which is interesting in view of the fact that Aschoff states it is not yet

definitely decided which side is more frequently involved. Ballowitz (4) in 1895 collected 213 cases of which 117 were on the left and 88 on the right and in 8 the side not stated. Gerard (5) in 1905 in a series of 278 cases says that the kidney was stated to be absent on the left in 109 instances and on the right in 76 cases. He further states that in his series 78 males showed an absence on the left and 44 on the right as compared with 31 females showing an absence on the left and 32 on the right. Winter (6) observed the condition 129 times on the left and 98 times on the right in a series of 237 cases and noted the same preponderance of the male sex for a left-sided defect. In my own collected series the preponderance of the male sex for the left side is in the ratio of 116 to 82, while the female sex shows a ratio of 87 to 79 in favor of the left side. Thus if the individual is a male the chances are strongly in favor of a left-sided defect, while in the female there is no preponderance in favor of either side.

*Condition of the existing kidney:*

The presence or absence of hypertrophy in the existing kidney has called for much consideration and in 195 of the 422 cases which I have collected this condition was noted. The degree of increase varies from "slight hypertrophy" to kidneys described as three times normal size. In some of these extreme cases, one wonders whether a part of the increase can not be explained on the basis of extreme congestion or some other pathologic condition. The increase in size is reported in most cases where microscopic examinations have been done, as being due

to hyperplasia, rather than a hypertrophy of the glomeruli and tubules. In most of the cases the kidney is reported as being of normal contour, although occasionally there is some distortion in the shape. Fetal lobulation does not appear to be noted in more instances than would be expected in an average run of cases. Much emphasis has been placed by some writers on the importance of a misplaced kidney in diagnosis of congenital one-sided defect, probably influenced by Polk's (7) famous case of removal of a single pelvic kidney. In my series only 20 cases showed a misplaced kidney, indicating that the condition is not frequent enough so that one is justified in expecting a misplaced kidney in these cases. Heiner, (8) who has fully discussed the subject of renal dystopia, concludes that renal dystopia is much more apt to be present where there is a congenital one-sided kidney defect than where both kidneys are well formed, so that in cases of misplaced kidney one may well be on the lookout for a congenitally absent kidney.

*Presence or absence of the ureter:*

The condition of the ureter on the affected side is an interesting phase of the subject. In 228 of my collected series of 422 or 54% of the cases, it was noted as absent, while in 42, or 10%, it was noted as present. In the remainder of the cases no mention is made of it. In 104 cases the ureteral orifice in the bladder is stated to be absent on the affected side. In several cases the site of the ureteral orifice was marked by a slight depression or even by a small diverticulum. Where no ureteral orifice is present on the

side of the defect, the other orifice is usually in its normal location and there is an asymmetry of the trigone. The ureter when present usually has no lumen or a lumen only part of its length and feathers out at its upper end, although in some cases a slight swelling is reported at the upper extremity. In some of these cases no microscopic examination of this swelling has been made, and it is possible that if this had been done these cases would be properly classed as aplasia. In other cases, this swelling has proved to be made up of connective tissue only.

*Renal vessels and adrenal:*

The absence of renal vessels on the side of the absent kidney has been noted in 100 cases of my series from the literature, and in many of those where vessels were present, they were simply small twigs distributing to the connective tissue, sympathetic ganglia, or sometimes to the adrenal on that side. In 46 cases of the 422 the adrenal was stated to be absent. When described as present it is usually of approximately normal shape although sometimes enlarged and flattened.

*Proportion in males and females with discussion of associated genital defects:*

All statistics show this condition to be more common in males than in females, statistics varying up to 4 to 1. My series shows a marked variation from this in that of the 381 cases where the sex was stated 198 were males and 183 females. Perhaps one explanation of this lies in the fact that the commonness with which deformities of the genital tract accompany this



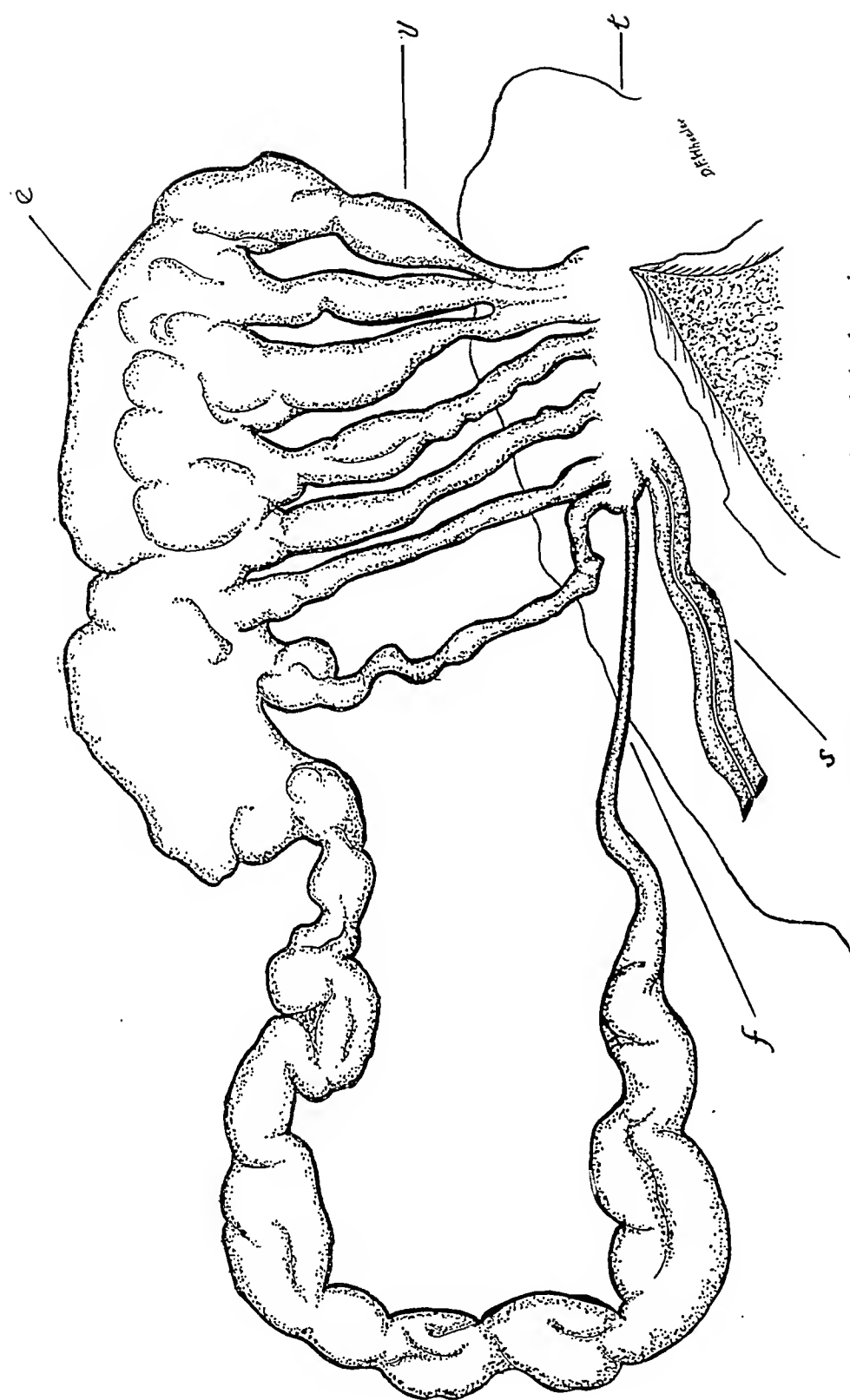


FIGURE 5. Dissection of the epididymis from Case IV. Interpretation of the legends: *v*, vasa efferentia arising from mediastinum testis; *e*, body of epididymis; *f*, fibrous cord marking termination of epididymis and attaching alongside mediastinum testis; *s*, spermatic artery and vein; *t*, body of testis with tunica albuginea opened one side.

condition in the female lends interest to female cases and leads to a greater frequency in the reporting of such cases. In my series 128 of the 183 female cases showed serious malformations of the genital tract. Eismayer (9) in 1923 collected 122 cases and classified them as to the type of defect. The commonest forms are unicornuate and bicornuate uteri of varying degree of development, the horn on the side of the defective kidney being less well developed. Didelphic uterus, septate uterus, and even absence of the uterus also occur. Malformations of the ovary are not common, case III (vide supra) being rather unusual in that respect, although there are a few cases of absence of the ovary and also of dysplasia of the ovary. Deformities or hypoplasia of the external genitals are rather common, and atresia of the vagina, absence of the clitoris, septate vagina, as well as malformations of the labia occur. Unusual terminations for a persistent ureter on the defective side are reported, both in the cervix and alongside the vagina.

Genital deformities in the male are less common than in the female, only 42 cases out of the 198 in my series stated to be male sex showing them. The commonest type of malformation is similar to that described in case IV (vide supra), although there are several cases of a rudimentary seminal vesicle on the affected side with a persistent ureter terminating in it, as well as cases of termination of a rudimentary ureter in the vas deferens. The testis is reported present on the affected side in all my cases, but often it is less well developed than its fellow, and occasionally is undescended.

#### *Embryological factors:*

The frequent association of renal agenesis and genital malformations naturally leads to a consideration of the closely linked embryology of the two systems. In this connection it must be remembered that the human being develops three distinct sets of excretory apparatus. The first of these, the pronephros, furnishes the duct system for the second organ, the mesonephros, but otherwise disappears entirely. The mesonephros, or Wolffian body, gives rise to important structures in the male, which are from cephalad to caudad, the efferent tubules of the testis, the vas deferens, the ejaculatory duct and seminal vesicles. The third excretory organ or metanephros develops as a budding off from the mesonephros and forms the anlage of the adult kidney. Simultaneously with this there develop two ducts known as the Müllerian ducts, which in the male give rise to no important structures, but in the female fuse caudad to form the vagina and uterus, and in their divided portion give rise to the Fallopian tubes. The sex glands arise separately from this duct system in a mass of tissue known as the genital ridge. The ureter arises as a bud from the Wolffian duct near its opening into the cloaca. The adrenal glands are linked in this development only by position, the cortex being of mesothelial origin while the medulla develops from the ectoderm of embryonic sympathetic ganglia.

Radasch (10) has pointed out that there are three possibilities of explaining renal agenesis: (1) A failure of the appearance of the metanephric bud, resulting in the absence of the kidney

even though the structures derived from the mesonephros were normal, (2) Appearance and early regression of the metanephros, (3) Failure of the pronephros, and therefore the mesonephros to appear. He reasons that since there is no uniform association of genital deformities, the first two propositions must explain absence of the kidney and that genital anomalies develop secondarily. While there can be no doubt that some cases of kidney agenesis can be explained by one of the first two theories, and cases of renal aplasia on the second theory, there is a fourth possibility which Radasch has overlooked, namely the appearance, but imperfect development of the mesonephros. Pohlman (11) discusses this possibility and advances the proposition that a failure of the Wolffian duct to unite with the cloaca may explain some of the combinations of anomalies which occur. This he argues would remove the stimulus for the formation of the metanephric bud and hence result in absence of the kidney and those structures in the male arising from the Wolffian duct.

Kornfeld (12), at the Institute of Embryology in Vienna, has carefully studied by serial sections a human embryo of 5 cm., vertex-heel length. He observed a complete left sided absence of the metanephric bud and the ureter and a deficient development of the Müllerian and Wolffian ducts, particularly in the caudal portions. Also there was no development of the left renal vessels. His embryo was a male, and from this he argues that if it had gone on to maturity there would have been absence of the left kidney, ureter, ejaculatory duct, seminal vesicle, vas

deferens and a portion of the epididymis. It will be noted that this case is entirely analagous to case IV reported above. The developing testis was not involved in the malformation. The fact that genital defects in the male always are most severe near the bladder and may diminish toward the testis seems to lend strength to the theory that a disturbance in the caudal portion of the embryo involving the Wolffian duct explains such anomalies. The greater frequency of genital malformations in the female associated with absence of one kidney can be understood by remembering that the Müllerian duct represents a later development than the Wolffian duct, and hence its chance of being involved in malformations is greater. In this case also the commonest malformations are those of the caudal portions, the uterus and vagina, while the Fallopian tubes are usually less involved.

*Association of multiple anomalies with kidney defect:*

As in all cases of disturbance of development, there are often serious malformations in other portions of the body, but the occurrence of multiple malformations outside the genital tract is much less uniformly the case than with many other types of deformity. Of the four cases presented above, three were perfectly normal except for the urogenital system. Of the 422 cases collected from the literature only 32 or 8% showed serious malformation outside of the genito-urinary tract. Where malformation is present it varies all the way from such monstrosities as sirenomelia down to hare-lip as in the case from this series. One case

of situs viscerus inversus associated with right sided absence of the kidney is noted. Thus it follows that the average patient who has only one kidney will show nothing in his external appearance to indicate his anomaly if a male, since usually the difference in the size of the testes is not great enough to occasion any suspicion of a defect in vas or seminal vesicle. In females the frequent malformation of the external genitals might serve as a warning in those cases where vaginal examination is done, but even in females many cases present nothing to excite any suspicion either of a malformation of the inner genitals or the absence of a kidney.

*Frequency of agenesis of the kidney:*

In considering the clinical interest of such a condition one thinks at once of its frequency as influencing its importance. Most of the older writers considered it as so rare that it could have little clinical interest to the physician. Ballowitz (4) saw it once in 617 cases. Morris (13) collected the statistics from four London hospitals and found that in 15,904 autopsies the condition occurred six times, or once in 2,650 cases. Anders (14) found at Pennsylvania Hospital 1 case in 1250 and at Philadelphia Hospital 8 cases in 6,240 autopsies. Such figures might be listed at length and they vary from one case in 4,000 autopsies to two cases in a series of 47 autopsies. At the University of Michigan three cases of true agenesis and one of renal aplasia have occurred in 2,580 autopsies. By adding up a total of 21 large series reported we find 108 cases in 139,346 autopsies or a ratio of 1 case in 1290

autopsies. It is interesting, however, to note that two of the three cases of total agenesis reported in this paper occurred in a series of 128 autopsies and within six months of each other. This emphasizes the fact that while the condition is relatively rare it is not so rare as to preclude the possibility of it occurring in the practice of any physician.

*Surgery of the unilateral kidney:*

A considerable number of instances of complete anuria with death have followed operations on a single kidney. Polk's (7) case of the removal of a pelvic tumor which proved to be the individual's only kidney has already been cited. Winter (6) in 1901 removed a large cystic kidney which proved at autopsy to be the only one present and at that time he collected 10 other cases from the literature with operative total removal of a supposed single kidney and death. In four of these, including his own, autopsy was performed and the agenesis of the other kidney confirmed. Two cases of traumatic rupture of a congenital unilateral kidney with death have also been reported. Venzmer (15) in 1921 collected 19 cases of operation on a one-sided kidney, and discussed the danger of operations on the one-sided kidney. In my collected series of 422 autopsies there are ten deaths following removal of one kidney and also six deaths following other operations on the kidney. Of these four were attempts to remove calculi and two pyelotomies for drainage. The death was of uremic type and in two of the six cases a total anuria was noted. These facts indicate that any operative procedure on a

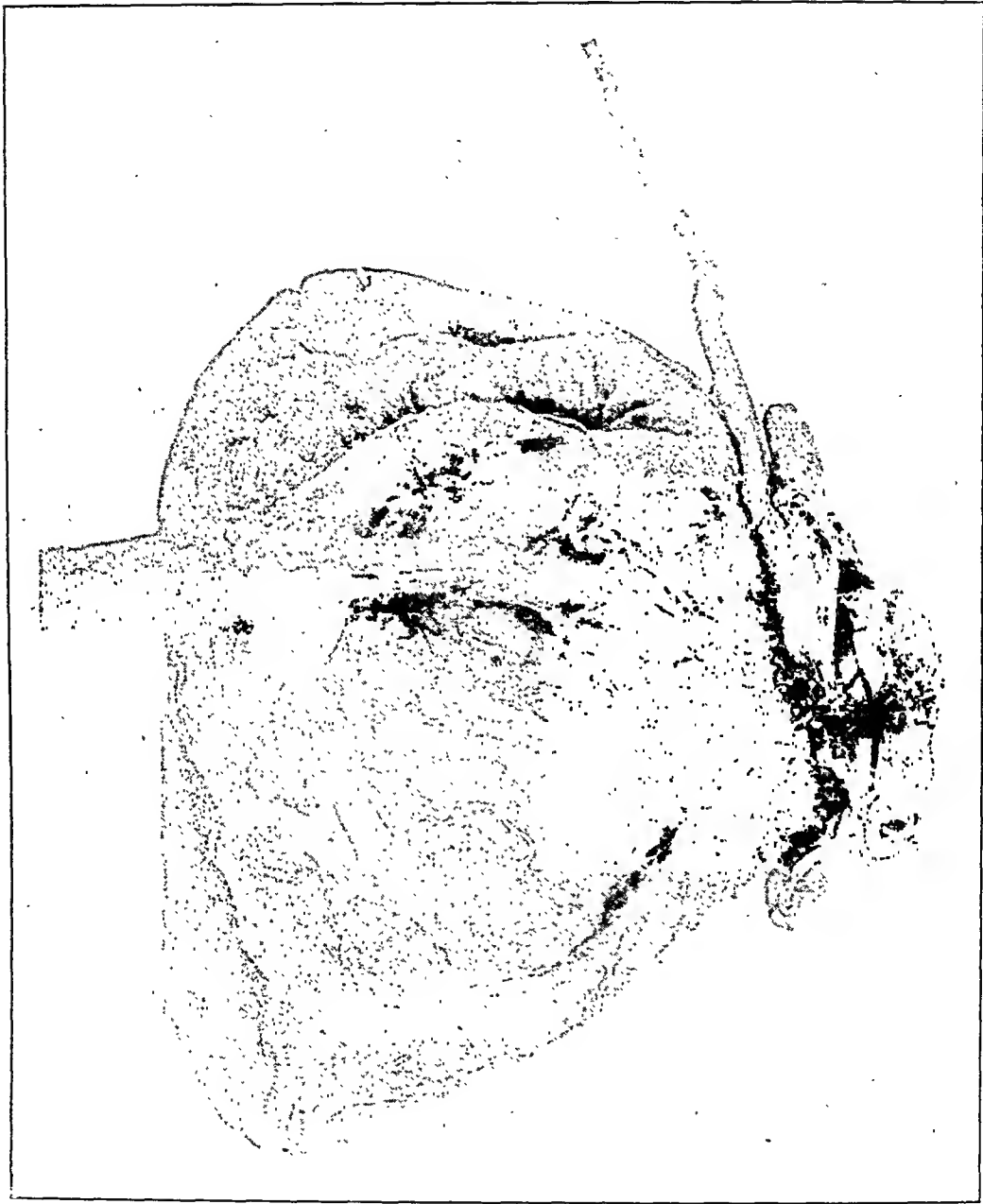


FIGURE 6. Detail of the posterior aspect of the bladder from Case IV. The left vas and seminal vesicle are absent and there is a small accessory lobe of prostate on the left side. The single, dilated ureter arises from the right side.

single kidney should be undertaken with caution. Against this there are at least five cases in the literature of complete anuria which was apparently due to obstruction of the ureter from a single kidney, successfully treated surgically. Of course in these cases one can only say that there was only one functioning kidney and that X-ray and other clinical means failed to demonstrate a kidney on the opposite side, but the clinical aspects of the case would not be altered by the presence of a rudimentary and non-functioning kidney. Of these operations, four were ureteral catheterizations and dilatation for stricture of the ureter, one of a ureteral transplant, and one the removal of a ureteral stone. The study of these few cases indicates that drastic operations on a single kidney are hazardous and should be undertaken only when more conservative measures are not applicable or have been inefficacious.

*Occurrence of disease in a unilateral kidney:*

Recently attention has been attracted to the frequency with which renal diseases occurs in cases of unilateral agenesis of one kidney. Anders (14) reported this finding in 46.5% of his cases. A study of my collected series of autopsy cases shows that renal diseases were mentioned in 96 instances or 22.6%, less than half the instance reported by Anders. Part of the variation may be explained by the fact that my series included a considerable number of cases overlooked by Anders and reported in anatomical journals as anatomical curiosities. In practically none of these is the presence or absence of renal disease in the existing kidney

noted, so that if the data had been complete undoubtedly my percentage would have been higher. Of these 96 cases 28 had some form of chronic nephritis, 23 stone in the kidney or ureter, 35 some other serious kidney diseases, pyonephrosis, hydronephrosis, tuberculosis, purulent nephritis etc., while in 10 cases the kidney disease was more or less incidental. While it is recognized that such a procedure has little statistical value, in order to get some basis of comparison a similar series of 422 autopsies from the files of the Department of Pathology of the University of Michigan were reviewed and 64 cases of kidney disease were found or 15%, of which 17 mentioned the kidney disease as an incidental occurrence. Thus without considering the fact that probably the percentage of cases of kidney disease in the cases collected from the literature is low, the percentage of kidney disease is a half greater in cases of one-sided defect than in a normal run of autopsy cases. It must be recognized of course that many of the individuals with a one-sided kidney defect never show any symptoms of renal insufficiency and in my series 50 or about 12% were reported as more than 55 years old. Certain writers have placed emphasis on the connection between kidney disease in childhood and agenesis of one kidney. In my series only five under 16 years of age showed kidney disease, which indicates that there is no unusual incidence of this condition in childhood.

The four cases presented in this paper illustrate the clinical situations which face the physician in such cases. In none of them was the condition di-

TABLE I  
*Compiled Statistics*

	Cases
Agenesis of one kidney.....	422
Sex stated as male.....	198
Sex stated as female.....	183
Occurring on the left side .....	218
Male .....	116
Female .....	87
Occurring on the right side.....	179
Male .....	82
Female .....	79
Remaining kidney said to be large.....	194
Ureter reported present on side of defect.....	42
Ureter reported absent on side of defect.....	228
Only one ureteral orifice described in bladder.....	104
Renal vessels reported absent .....	100
Associated malformations of female genitals.....	128
Associated malformation of male genitals.....	42
Adrenal absent on defective side.....	46
Remaining kidney misplaced.....	20
Remaining kidney diseased.....	96
Chronic nephritis .....	28
Stone in kidney or ureter.....	23
Other forms of kidney disease of serious nature.....	35
Kidney disease an incidental finding.....	10
Operative removal of single kidney.....	10
Other operations with death.....	6

agnosed clinically. In three of them the kidney deficiency had produced no clinical symptoms. One was a child, a below par individual, with other malformations, dying from diarrhoea of infancy, with an acute nephritis which was considered of minor importance as a cause of death. Another was a young girl, dying from an acute infection with septico-pyemia, the so-called malignant furuncle of the face. The third was an old woman dying of skull fracture. In the case of the old woman inflammatory foci are mentioned in the kidney, but they were of no clinical significance in her case at the time of her death from other causes. In none of these cases are there urinary findings or clinical symptoms which would in

any way indicate that the one kidney existing was experiencing any difficulty in performing the work of two kidneys.

The fourth case, however, presents features of clinical interest. While in some ways a typical case of chronic nephritis, there are certain features which differ from the usual findings. The course of the disease from the earliest clinical symptoms to uremia with advanced secondary contraction of the kidney was rather short, and at no time was there the development of the usual oedema. Instead, relatively early in the disease there was an unusually high blood pressure with marked hypertrophy of the heart. In addition to this, the autopsy showed a most unusual degree of arteriosclerosis, particu-

larly in the aorta and coronary vessels. A number of cases from the literature report cardiac hypertrophy, but even in those with fairly complete clinical histories the blood pressure is practically never given, so no statement can be made as to the frequency of this finding. At the time of the patient's admission the kidneys failed to eliminate any dye, the concentration power was practically nothing, and the non-protein nitrogen of the blood was high and rapidly increasing. These findings indicate that, as might be expected, in cases where one kidney is congenitally absent, the other is not only more subject to disease, but that disease of the kidney when present tends to run a more fulminating course. While the danger of drawing conclusions from an isolated case is freely admitted, it appears that the prognosis in kidney disease is more grave in cases where there is only one kidney present.

The clinical diagnosis of a unilateral absence of the kidney is not a simple matter, and there is at present no way in which one can determine whether the condition is a true absence or a case of non-function of one kidney, except by an exploratory operation. Winter (6) after his experience in removing a single kidney recommended that in all cases where it was impossible to determine by other means the presence of two kidneys, an exploratory incision should be made over the other kidney before operating on a diseased kidney. Cystoscopy will in many cases reveal the presence or absence of the second kidney, but the mere finding of two ureteral orifices is not sufficient as in many of the cases the ureter on the deficient side persists. If the urine

can be seen coming from the openings the presence of both kidneys is indicated but the degree of function on the two sides can be determined only by ureteral catheterization and dye injection. The association of any genital defect if known should place the physician on his guard for the absence of one kidney, particularly if the defect is of the type described as being frequently associated with this malformation.

The chief clinical importance of this condition lies then in the fact that the single kidney present is more subject to disease, and that disease of that kidney is more difficult to treat. At the present time, most of these cases occur as "autopsy surprises." There should be a higher accuracy of diagnosis, and this is possible only when physicians bear in mind that every case of kidney disease may be one of a congenital unilateral kidney. Having diagnosed the condition, the physician should recommend surgical operations only when absolutely necessary. Often such an individual will come in with anuria, and in such a case something obviously must be done, but the operation undertaken should be the most conservative possible. Any patient coming in with a suddenly developing anuria, particularly if associated with renal colic should awaken a suspicion of this condition on account of the frequency of stone in a single kidney, and there is considerable importance attaching to a recognition before treatment is instituted.

#### *Summary*

(1) Agnesia or total absence and aplasia, or failure of functional development, occurring in one kidney, while



rare, is a condition which may occur in any physician's practice. The computed frequency from a large series of reported instances is one case in 1290 autopsies.

(2) A series of 419 cases of agenesis of one kidney have been collected from the literature. In addition to these three new cases of agenesis and one case of aplasia have been reported, together with the clinical findings.

(3) The defect occurs somewhat more frequently in the male than in the female, but there is not the marked male preponderance reported by many writers. In males the left side is more frequently affected in the ratio of 3 to 2 while in the female the occurrence is practically equal on the two sides.

(4) Genital malformations are associated with agenesis of the kidney in 70% of the females, the most common being those due to imperfect development of the Müllerian ducts—atresia of the vagina, septate vagina, septate uterus, didelphic uterus, bicornuate uterus, and unicornuate uterus. The side of the kidney defect shows a more rudimentary condition than the opposite side. In the male genital malformations were present in 22% of the cases, the most common being an absence on the affected side of the Wolffian duct derivatives—the ejaculatory duct, seminal vesicle, vas deferens, and

the tail and part of the body of the epididymis. The genital glands are rarely seriously involved.

(5) The ureter was reported as absent on the affected side in 54% of the cases and present in 10% of the cases. The renal vessels were reported as absent on the side of the kidney defect in 23.7% of the cases. The corresponding adrenal was absent in 10% of the cases.

(6) The existing kidney in a case of unilateral agenesis is more subject to disease than when two kidneys are present, kidney disease being noted in 22.6% of the reported cases as against 15% in an average run of autopsies.

(7) Surgical operations on a unilateral kidney are apt to be followed by anuria and death, and when undertaken should be as conservative as possible.

(8) Kidney disease offers a poorer prognosis in the case of unilateral kidney than when two kidneys are present.

(9) Congenital absence of one kidney is at present seldom diagnosed clinically. Its recognition depends upon a realization by the clinician of the possibility of its presence and a search for evidence of the condition, since it usually presents no clinical symptoms pointing directly to its existence.

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# The Embryohormonic Relations of the Thyroid Gland to Ectodermal Tissues

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THE correlation of function among the endocrine glands has been a trying problem; but recent work is paving the way to a better understanding. Naturally, the teaching of this subject has been difficult and the student has been confused because he has no mental splint by which he can fix a systematic scheme for their study. In these articles I will endeavor to show how the subject may be made easier through the medium of embryological origin of tissues, and if this is done, the symptomatology of various endocrinopathies is more easily understood.

During a course of thirteen years, confidence in this scheme of viewing the endocrine relationship has become greater as individual portions of it have been proved experimentally.

The basis of my plan for correlating the endocrine glands rests upon the selectivity of each secretion on particular tissues according to their embryological origin.

Impetus has been given to the study of endocrinology by observations on the human constitution. Our knowledge of the endocrines makes it natural to link this study of the constitution with the specific influence of the ductless glands on the body make up.

A well known example of this specific influence is that of the pituitary gland on bone development. Another is that of the thyroid on brain development and function. That manifestations of racial body characteristics and morphology are influenced by the endocrine glands is too well known to need further emphasis. Bauer (1) especially has emphasized the constitutional study of disease; and no textbook on the endocrines is now complete without a chapter devoted to this phase of the subject.

As constitutional inheritance is studied, the impression is gained that certain groups of cells have inherent characteristics and react in specific ways to bodily (i.e. chemical) influences. It is this point that I wish to emphasize in order to provide an understanding of the selective action of the endocrine glands, disturbances of which may produce at times, anomalies such as cretins, dwarfs, giants, etc.

It is obvious that constitutional inheritance predisposes the individual to certain diseases and it is equally obvious that in a specific case certain tissues manifest this tendency.

There are many clinical examples of the selective action of the ductless glands on certain tissues. The func-

tional and genetic relationship of the suprarenal cortex to the sexual glands, the selectivity of the suprarenal medulla secretion on the sympathetic nervous system are two examples.

We are familiar with the fact that endocrine diseases produce a variable picture in different individuals. Hyperthyroidism for instance, of the same degree of severity in two individuals manifests itself in certain tissues with a varying degree of severity. This can only be understood by constitutional inheritance. The so-called local "gen" with its constitutional inheritance determines the predominant symptomatology.

Discussing with others the embryological correlation of the endocrine glands through selective action, I find that the main difficulty in understanding the hypothesis is that the impression is gained that the endocrine gland in question has a selective action on the tissues from which it originates. For instance it is thought that the pituitary, being ectodermal in origin has a selective action on ectodermal tissues. This is not necessarily true.

In studying the selective action of certain of the endocrine glands, the thyroid will be considered first, the pituitary second and the suprarenal cortex, third. It is possible that later the other glands will be considered but for the present, in order to lay a foundation, just those above mentioned will be studied.

### THE THYROID GLAND.

#### *The Thyroid has a Selective Action on Ectodermal Tissues.*

The thyroid gland is developed from the entodermal layer, but has a selective

action on ectodermal tissues. These tissues are:

- Skin
- Hair
- Nails
- Sebaceous and sudorific glands
- Mammary gland
- Eye
- Auditory organ
- Central nervous system
- Sympathetic nervous system
- Suprarenal medulla
- Olfactory organ
- Enamel of teeth
- Pituitary gland

According to the hypothesis the function of the thyroid gland is reflected in these ectodermal tissues.

Taking as an example hypofunction, severe myxedema or cretinism, the changes and symptoms in these tissues by this disease will be mentioned.

*Skin.* The sebaceous and sudorific glands are derived from the ectoderm and thyroid hypofunction produces a lessened *sebaceous* and *sudorific gland* function. It is not surprising therefore that we encounter many skin changes in hypothyroidism. Cutaneous dryness is frequent. The sudorific action of pilocarpin is lessened or entirely absent. (Falta) (2). The *hair* is very dry and hypothyroid baldness is not uncommon. The sparseness of the hair is not entirely confined to the head but the axillary hair, trunk, thighs etc., are also involved. The *nails* are striated, brittle and atrophic. Janney and Henderson (3) state that at least eighty per cent of hypothyroid individuals have nail involvement. The softness of the nails produces a sensitive-

ness which is very troublesome. Scleroderma, psoriasis, ichthyosis, etc., are very frequently seen in hypothyroidism. It is surprising how frequently psoriasis, eczema, and dermatitis of various sorts will give the first clue to the presence of hypothyroidism. Recently I noted the incidence of goiter with psoriasis and the number is remarkably high. That great benefit is derived from thyroid medication in many skin diseases is well known to dermatologists. That scleroderma may follow hypothyroidism as the result of thyroidectomy is well known. Why is it that only a few have this disease as a result of hypothyroidism? The explanation can be found in constitutional inheritance. In this case, the skin as a local gen shows an inherent constitutional weakness, thus bearing the brunt of the hypothyroidism in the form of scleroderma. Obviously the sebaceous and sudorific glands are severely involved. This local gen weakness may of course be manifested in other ectodermal tissues and holds true for all endocrine diseases. *The mammary glands* are usually large but this is due to the large amount of fat present and not to the lacteal tissue which is poorly developed.

*Eye.*—The association of hypothyroidism with *eye* conditions is a very interesting study and the undoubted influence the thyroid secretion has on the eye makes the study of great importance. Hypothyroidism would theoretically result in degenerative eye changes. That this is true clinically, is well known. Athyreosis is frequently associated with agenesis or hypoplasia of the uveal tract with resulting blindness. Corneal ulcers are also not in-

frequent and I have seen a case of congenital cataract with corneal ulcer in association with goiter in a girl who has since developed true exophthalmic goiter. She likewise has congenital nystagmus and is feeble minded. Zentmayer (4) says that keratitis, corneal ulceration, conjunctivitis and blepharitis may be produced through thyroidectomy. Atrophy of the whole eye has been observed. (V. Szily and Poos) (5). Radical thyroidectomy results at times in marked eye disturbances of a degenerative nature. Cataract is not infrequent. Zentmayer (4) quotes Petzetakis as saying that hypothyroidism leaves the sympathetic without the normal stimulation of the thyroid, and as a consequence vagotonus results.

*Auditory organ.* Hypothyroidism frequently produces changes in the function of the auditory organ, both in infancy and adult life. "The epithelium of the internal ear is derived from the *ectoderm*. The epithelium of the labyrinth at first is composed of a single layer of low columnar cells. At an early stage, fibers from the acoustic nerve grow between the epithelial cells in certain regions and these become modified to produce special sense organs. These end organs are the cristae ampullares in the ampullae of the semicircular canals, the maculae acusticae in the atriculus and sacculus, and the spiral organ in the cochlear duct.

*Mesenchyme* surrounds the labyrinth and is differentiated into a fibrous membrane directly surrounding the epithelium, and into the perichondrium of the cartilage, which develops about the whole internal ear. (6) We see from this that the ear proper is

ectodermal in origin while the source of the bony labyrinth surrounding the ear proper is derived from the mesoderm. To my mind this is important in determining the origin of otosclerosis, there being a question as to whether the thyroid or pituitary is responsible, but this cannot be discussed here.

The association of deafness with cretinism is very well known. Some ascribe this to cortical deafness but this does not explain the deafness that adults have who developed hypothyroidism in later life. The pathological changes found in the auditory organ in cretinism are many and diverse. Alexander (7) has reviewed the findings of many authors and the degenerative nature of the lesions reported is striking. Many photographs of the auditory organ in its finest detail are given in this thorough and extensive review.

Barlow (8) in studying the vestibular nerve function in fifteen cases of myxedema found that there was a lessened response to stimuli. I (9) have reported twenty-four cases of hypothyroidism associated with vertigo and deafness. Eighteen of these cases who were not totally deaf showed marked improvement in hearing as well as the disappearance of the vertigo upon taking thyroid extract. These individuals did not show any striking hypothyroid signs and for this reason the association had not been previously thought of.

We may safely say that degenerative changes in the auditory organ are the rule in hypothyroidism.

*Central Nervous System.* The influence of hypothyroidism on the central nervous system is quite familiar to everyone. The slowing of mentality

so frequently a part of the myxedematous picture produces an obvious association between thyroid function and this portion of the ectoderm—the central nervous system.

The pathology of the central nervous system in hypothyroidism depends on the time when the hypothyroidism takes place and upon its severity. Naturally the greatest pathology is found in congenital conditions such as cretinism. Idiocy and feeble-mindedness are prevalent in endemic localities. Mental backwardness is manifested early in these individuals. Older children have difficulty in acquiring knowledge and have a low intelligence quotient. The memory is poor, they are slow and sluggish in their actions. Depression and melancholia is frequent. The relation of the thyroid to certain mental diseases is at present an unsettled one, but that it influences the psyche seems likely.

Non-development of the convolutions of the brain is frequent. More emphasis is being placed by pediatricians and endocrinologists on the mental symptoms of hypothyroidism. These patients do not notice objects about them and they creep, stand and walk at a later age. We have frequently encountered psychoses in goiter patients and no doubt this association is noted in many goiter clinics. Phillips (10) observed goiter in twelve per cent of patients suffering from psychoses.

We find, therefore, that hypothyroidism is associated with degenerative changes in the central nervous system and the normal function of this system must be dependent, in part at least, on normal thyroid function.

*The suprarenal medulla and the sympathetic nervous system.* A definite relationship exists between thyroid function, the *suprarenal medulla*, and the *sympathetic nervous system*. Emphasis must be placed on the fact that the suprarenal medulla is ectodermal in origin, in contrast to the suprarenal cortex which is mesenchymal in origin. The medullary portion as we know produces epinephrine.

Many clinical facts demonstrate the relationship between the thyroid gland and the suprarenal medulla. Theoretically it will be noted that hypothyroidism would result in a decreased function of the sympathetic nervous system and suprarenal function. So far as the function of the latter is concerned arguments are still progressing as to whether the epinephrine is given off only during emergencies or whether it is constantly given off in low concentration. At any rate, it is a well known fact that hypothyroid individuals have a greater tolerance for epinephrine than normal individuals. Certain it is that epinephrine has a definite and selective action on the sympathetic system. The literature is full of experimental and clinical proof that the sympathetic nervous system gives a lessened response in hypothyroidism. Hoskins (11) has recently stated that in the present state of our knowledge, perhaps the most plausible assumption is that epinephrine consistently and generally exerts a biphasic effect as it has been shown to do in cases of intestinal peristalsis, uterine contractions and blood vessels in muscles. Hyman and Kessel (12) in a series of articles show the close relationship between the

thyroid and involuntary nervous system.

*Olfactory Organ.* The sense of smell is diminished in hypothyroidism. Some believe this to be central in origin and not peripheral. The importance of this relation to the selective action of thyroid on this ectodermal tissue is not very great. However, on theoretical grounds it would be the result of central and peripheral organ involvement.

*Enamel of teeth.* The *teeth* in hypothyroidism are notoriously carious, dentition is delayed and if hypothyroidism continues second dentition is affected.

*The pituitary gland.* The relationship of the thyroid to the pituitary is a most important one and as so much depends upon showing the relationship, this phase will be discussed more fully. It is well to state that according to the opinion advanced here, hypothyroidism would result in hypopituitarism and hyperthyroidism would produce hyperpituitarism. Let me emphasize, however, that as far as the pituitary is concerned, results from hypo- and hyperthyroidism are not as severe as that seen in primary pathology of the pituitary gland.

Trautman (13) has dealt at length with the influence of thyroidectomy on the pituitary. He used thirty goats in his experiments. Thyroidectomy in these animals resulted in marked alterations in all three parts of the pituitary. He concludes that there exists an inner physiological relationship between pituitary and the thyroid. He believes that the complete or partial elimination of the thyroid causes an actual patho-

logical alteration in the properties of the blood which acts in a harmful manner on the different parts of the pituitary.

The alterations are of a degenerative type, thus proving that the pituitary cannot functionate vicariously for the thyroid. Evans (14) from his work on animals, believes that pituitary function is really reduced after thyroidectomy, though the pituitary is not smaller, and indeed, undergoes a transitory enlargement. He quotes Degener to the effect that the peculiar enlargement of the anterior pituitary after thyroidectomy does not represent the assumption of vicarious function. Mammalian experiments made by Smith and Graeser and by Flower and Evans, show that hypophysectomized animals cannot grow if given thyroid but that thyroid-free animals possessing the pituitary will grow normally or better than normally if the pituitary hormone is given parenterally along with thyroid therapy. He goes on to say that in one case we convey the growth hormone directly, in the other we furnish the animals own pituitary with a material needed directly or indirectly for its normal function. He believes that the thyroid is essential for pituitary normality. This is the real cause for dwarfism in the cretin.

Hoskins and Hoskins (15) conclude from their series of experiments on frog larvae that removal of the thyroid hastens growth, causes hyperplasia of the pituitary and prevents metamorphosis. Smith and Cheney (16) believe that the anterior lobe preparations used by Hoskins and Hoskins contained an unusual amount of iodine and displayed an altogether unique activity.

From their own work they conclude that the evidence indicates that a similarity of response is not evoked by thyroid and pituitary administrations.

Allen (17) found that in normal tadpoles in which the pituitary had been ablated, that when the anterior lobe was implanted the thyroid glands were restored to almost normal size. Berblinger (18) examined the pituitary in five people with hypofunction of the thyroid dying from intercurrent disease. He found an increased number of chromophobe cells, the cells are richer in protoplasm than normally. In the syncytial cells degeneration of the nucleus was seen. In three of the five cases the pituitary was heavier than normal. He says this increase in weight is only due to the increase of chromophil cells. He does not believe that the enlargement of the pituitary after thyroidectomy is compensatory. Vallillo (19) found that the histological observations on the prehypophyseal parenchyma of goats and horses previously deprived of the thyroid showed modifications, on the whole equal in all cases. These modifications are characterized by increase of the eosinophil cells, or by their regressive alterations. The presence of new elements determines the increase in the weight of the gland. Friedman (20) says that the pituitary appears to show histological changes in Graves disease similar to those of hyperpituitarism and in myxedema to those of hypopituitarism, and that chromophilia of the anterior lobe is characteristic for Graves disease; chromophobia for myxedema.

Cooksey (21) concludes from experiments on tadpoles that feeding thy-



roid extract produces a diminution in the size of the anterior pituitary.

Janney (22) says that the pituitary regularly hypertrophies in animals following thyroidectomy, and sometimes in myxedema.

Schoneman (23) who is extensively quoted on thyroid-pituitary relationship, reported that in one hundred and twelve cases of goiter, the pituitary was atrophied in proportion to the degenerative changes found in the thyroid. Connective tissue overgrowth, hyaline degeneration, colloid formation, vascular and chromophilic hyperplasia are found.

de Coulon (24) reported microscopic hypertrophy but diminution of the glandular tissue.

According to Falta (25) in myxedema the pituitary is commonly altered. He quotes Boyce and Beadles as finding enlargement of the pituitary as did also Ponfick. Quoting another case of pituitary enlargement with colloid degeneration of the protoplasm, Falta says that in other cases there has occurred a pronounced sclerotic degeneration of the glandular pituitary, (2nd. Case of Ponfick) or cystic degeneration. (Sainton and Rothery and others). In myxedema adutorum the pituitaries present changes of a strumous character or simultaneously with these, changes of a chronic inflammatory nature. He says in italics "The goiter poison therefore works deleteriously on the hypophysis."

Rogowitch (26), Stieda (27) and Hofmeister (28) found hypertrophy of the pituitary after thyroid removal in rabbits.

Eichhorst (29) found degenerative changes in hypothyroidism.

V. Cyon (30) found strumous alterations in the pituitary of St. Bernard dogs after thyroidectomy.

Hammett (31) who has made extensive studies on endocrine gland relationships concludes as follows concerning the thyroid and pituitary relationships. "1. Thyroid deficiency conditions a consistent hypertrophy of the hypophysis in the male but not in the female. 2. The size and presumably the activity of the hypophysis is specifically related to the activity of the thyroid when this exceeds the usual limits in either direction. 3. This relationship is conditioned by gonadal incretory activity in the female but not in the male."

He tries to dispute the interpretation placed on Flowers' and Evans' work. Hammett assumes that the enlarged pituitary means increased functional activity. Such an assumption is not justified according to the clinical data and other reported experimental work. An enlarged and altered pituitary does not postulate increased function any more than a goiter of the colloid type represents increased functional activity. Until the pathology of the pituitary is better understood hard and fast rules cannot be drawn. It would be best, it seems to me, to use the clinical data we have to determine the functional activity of the pituitary in hypo- and in hypertrophied states.

Naturally more of these findings could be quoted but this is sufficient to show the opinions held. In summarizing the changes found in the pituitary in hypothyroidism the available evidence points to a *degenerative enlargement* of the pituitary. At the present time we are not certain as to the mean-

ing of the cell changes found in the pituitary and therefore cannot definitely interpret the significance of the cell pathology. It is certain that this enlargement does not represent functional activity, as is evidenced by the small stature of cretins and infantile hypothyroid individuals. Why do we find delayed osseous development and under developed sexual glands and organs in cretins if there is hyperfunction of the pituitary in hypothyroid states? These are all signs and symptoms of hypopituitarism. The fact is that the pituitary (an ectodermal tissue) is affected by hypothyroidism in the same manner as all other ectodermal structures and as a result of this many secondary changes due to pituitary disease supervene. This will be more fully discussed in the article on the pituitary hormone.

I will but briefly review some of the many symptoms found in the ectodermal tissues in hyperthyroidism. Naturally the tissues should show evidence of hyperactivity.

I wish to again emphasize that according to the inheritance characteristics of the local gen (referring to skin, nervous system, auditory organ, etc.) the manifestations vary in different individuals, for hyperthyroidism of the same intensity measured at least according to our present day standards, does not produce the same picture in every individual. It is a well known fact that certain systems suffer more than others which can be accounted for only through inheritance liability of these systems.

*Skin.* Great increase in the *sebaceous* and *sudorific gland* function is present in hyperthyroidism, so that as

a result the skin is soft, oily and moist. It is of a delicate texture. These individuals like winter months best. Marked erythema is present. One of the very frequent symptoms complained of by hyperthyroid patients of severe and milder types is urticaria.

*Hair.* Early graying of the hair is frequent. It is usually abundant and oily, although many have loss of hair.

*Nails.* The nails are long and tapering. I have noticed how quickly the nails grow in hyperthyroid individuals.

*Mammary glands.* The mammary glands are hypertrophied and the male gland has been known to secrete colostrum.

*Central Nervous system.* Involvement of the central nervous system in hyperthyroid states is very evident. A rapid flow of ideas, change in character, and mental condition is often an early sign of hyperthyroidism. Irritability, excitability, insomnia and restlessness are frequent symptoms. These patients are never restful, but looking for a continual change. They are impatient, super-sensitive and often cry for trivial reasons. Apprehension and anxiety are common features. Cases of neurasthenia with rapid heart action and other neuroses, are frequently due to an overlooked goiter. One wonders how many of these cases are really abortive or mild forms of hyperthyroidism with the greatest manifestation in the sympathetic nervous system and tissues affected by this system. Some of these hyperthyroid individuals can carry on great mental labor and are never satisfied until the goal is

reached. As Howard (33) says their mental condition is aptly described by the term "chorea of ideas," Moebius (34) compares the mental state to a mild alcoholic intoxication.

*Suprarenal Medulla and Sympathetic Nervous System.* That the sympathetic system is hyperactive in hyperthyroidism is well known. The irritability of the sympathetic system is shown by the vasomotor flushing, diarrhea, digestive disturbances, rapid heart action, etc. Urticaria is frequently present. Hyperthyroid patients are very sensitive to epinephrine. (Goetsch test). De Lucas (35) says that the sensitivity to epinephrine is modified in thyroid conditions and is roughly parallel to the activity of the thyroid. Hyperthyroid individuals suffer from asthma, hay fever, and other forms of sensitization diseases.

*Pituitary gland.* Here again is an important and interesting relationship. It goes a long way to explain many symptoms seen in thyroid disease. Theoretically hyperthyroidism would result in hyperpituitarism. Some of the facts quoted in regard to the pituitary in hypothyroidism hold good in hyperthyroidism—such as the feeding experiments of Smith and Evans.

The incidence of goiter in acromegaly is too well known clinically to need reviewing of the literature.

Davidoff (36) found a palpable or definitely enlarged thyroid in twenty-five of a hundred patients with acromegaly.

Cushing and Davidoff (37) in their recent studies conclude that the increased metabolism frequently found in acromegaly is due not to the thyroid but

to the pituitary disturbance. However, a final answer cannot be given, they say, until the active principle of the anterior lobe is isolated. They cite three cases of goiter with acromegaly who had thyroidectomies,—the thyroid gland showing colloid changes. They conclude that the evidence, despite the drop in metabolism post-operatively shows that the goiters were not active. They furthermore state that it must not be forgotten that a number of cases of exophthalmic goiter have been described as coexistent with acromegaly. They tend to question the dependability of the diagnosis. In concluding this phase of the study they say "But all told, there is nothing in the evidence so far that would contradict the possibility that primary hyperthyroidism and primary hyperpituitarism may co-exist in the same patient."

In concluding the article, they say that acromegaly is often accompanied by a palpably enlarged thyroid and by symptoms suggesting thyreotoxicosis to which the increased metabolic rate has generally been ascribed and that the chromophilic cells of the anterior lobe of the pituitary body secrete a substance which not only contains the hormone of growth, but which is capable of raising the metabolic rate. Whether the hypophyseal principle under these circumstances acts as a stimulus to metabolism directly on the tissues or only through the intermediation of the thyroid, they say cannot as yet be positively stated, although there are reasons to believe that it may act independently. It is obvious that these facts if considered objectively could just as well receive the other interpretation, namely, that in the cases they quote, the

thyroid itself was basically responsible for the condition and that the pituitary changes were concomitant.

I have two cases at present that are definitely acromegalic individuals with primary hyperthyroidism.

Hofstaetter (38) believes that some of the symptoms of exophthalmic goiter can better be explained by an injury of the pituitary than by hyperfunction of the thyroid gland. Some of these are polyuria, polydipsia, some of the trophic disturbances, disturbances in growth, fat deposition and the insomnia. I would add that the glycosuria, hypertension, lymphocytosis and headaches were due to the pituitary but I cannot see how the insomnia can be ascribed to the pituitary.

Hyperthyroidism should result in an accelerated growth in height and a premature closure of the epiphysial structures. So it is found clinically. Holmgren (39) has shown this to be true.

Ballet (40) reported a nineteen year old girl with hyperthyroidism and gigantism.

The skeleton of the youthful hyperthyroid is slender, resembling somewhat the eunuchoid type and the long tapering fingers is a frequent clinical finding. It is also noted that the joints show an abnormal amount of mobility in all directions, these individuals often performing remarkable acrobatic feats through the mobility of their joints.

Anders and Jameson (41) review the relationship between the thyroid and pituitary. In one part they say that the pituitary in myxedema is anatomically a hypertrophied gland, but

physiologically an atrophied one. They reviewed two hundred and fifty cases of acromegaly and of this number changes in the thyroid were mentioned in sixty-eight. They believe that their studies indicate that the hypothyroidism is more commonly associated with acromegaly than hyperthyroidism and those combined cases which manifest myxedematous features are decidedly improved as the result of the use of thyroid preparation. It is my opinion that the stage of acromegaly has also a great deal to do with this and the state of the sex glands is also of great importance. The function of these is markedly diminished in later stages of acromegaly and this is followed by lowered metabolism.

Summarizing the findings in hyperthyroidism, the available evidence points to a hyperactive pituitary.

The next article will discuss the selective action of the pituitary.

### *Summary*

The study of the human constitution is inseparably linked with the endocrine glands.

A better understanding of glandular relationships can be had from an embryological study. Certain of the endocrine glands have a selective action on tissues depending upon their embryological origin.

The thyroid gland has a selective action on ectodermal tissues.

This embryological correlation agrees with the facts at hand and gives an easy understanding of the symptomatology and glandular interrelationship.

# The Effect of Pituitary Administration on Growing Dogs\*

By W. G. DOWNS, JR., *Department of Anatomy, University of Michigan.*

THE following investigations were instituted for a study of the relationship between the glands of internal secretion and the development of the dental mechanism. While the dental phase was the one of primary interest, careful records were kept of a number of other observable results. Although the findings for the effect of hypophysis on the development of the dental mechanism were negative, (Downs, 1927) some very interesting and somewhat surprising systemic results were obtained. It is these, because of this fact, which will be recorded here.

The experimental animals used were puppies with an average age of four weeks at the beginning of the experiments, none being over six weeks old. The animals were mongrels, and consequently no information was obtainable as to their genetic makeup. To as far as possible offset the untoward effects of different blood-strains, the animals were handled by litters, so that a given experimental animal and its accompanying control were of the same age and parentage. As the investigations

were primarily dental in character, no regard was paid to sex.

The experiments were divided into two series. In the first series, pituitary extracts were fed (Armour & Co's dried ox-gland). In the second series, the animals were injected with the glycerin suspension of the pituitary extracts (Parke, Davis & Co.). Throughout both experiments medication was administered at regular intervals, each animal in both series was given one dram of cod-liver oil (Mead-Johnson & Co.'s) once a day to offset the possibility of rickets and all of the animals were wormed when the need for it became evident in any of them. All animals were weighed and carefully examined every five days. Daily note was made of any changes in the outward appearance or behavior of any of the animals, and both during the experiments and at the time of necropsy for all experiments, all unusual conditions noted were compared with the evidence obtained from the literature.

For the first series, five litters of four puppies each were used. In each litter one dog was fed the extract of the anterior lobe of the hypophysis, one that of the posterior lobe, one received whole-gland extract, while one, the control animal received a normal

\*The experimental work involved in these investigations was pursued in large part at the Department of Anatomy of Indiana University, Bloomington, Indiana.

diet only. The dosage was computed so as to be nearly proportionate to the maximum dosage for a human of average weight. This dosage was, in the case of the anterior lobe extract,  $\frac{1}{2}$  grain, of the posterior lobe extract,  $\frac{1}{40}$  grain, and of the whole gland  $\frac{1}{2}$  grain, each 3 times a day. Beginning four weeks from the initiation of this experiment entire litters were killed at intervals of four weeks. The animal was examined for gross changes, the tissues of the mouth, the hypophyses, thyroid and parathyroid glands were studied microscopically, and the vertebrae and tibias, as representing typical short and long bones, were cleaned and studied by the silver nitrate method of Bills (1925) for variations in calcification. The tissues for microscopic examination were uniformly prepared, having been fixed in 10% formalin, imbedded in paraffin, stained with chloral hematoxylin and counter-stained with eosin.

No definite variations in size, number, form, nuclei or standing qualities of the various cellular constituents could be observed in either of the litters. This does not coincide with the results obtained by Goetsch (1916), who obtained positive results from feeding experiments. It is felt, however, that in these experiments the size of dosage used and the period over which the experiments were conducted should be adequate to bring out any changes which might occur in such animals as dogs by glandular medication per os. The examination of the bones likewise yielded entirely negative results. There was, furthermore, no typical variation in temperament, behavior, hair color or texture

which might not be expected of animals of such uncertain genetic origin. It is felt that the findings from the experiments in feeding the pituitary extracts, as regards bony growth, general metabolic changes, and changes in the gland itself, were entirely negative.

Such was not, however, the case with the second series. These were injection experiments. As has been noted the type of animals used, methods of handling, proportionate dosage, and methods of examination were identical with those used in the first series. For these investigations six litters of three puppies each were used. In each litter, for the first six weeks, one dog was injected with three minims of antuitrin (Parke, Davis & Co.) twice daily. One dog received three minims of pituitrin (Parke, Davis & Co.) twice daily. One dog, the control animal, received three minims of sterile water twice daily to offset any possible differences due to the traumatic effect of the injections. After six weeks of this dosage, although no marked untoward systemic effects had been noted, it was felt that the dosage was disproportionately large, and the dosage was reduced to one minim in each case, twice daily.

At the beginning it was intended that these animals be killed and necropsied at the same intervals as those in the preceding series. On the twenty-eighth day one litter was killed and on the fifty-sixth the next. At about the sixtieth day a number of the remaining animals began to develop symptoms of worms. All of the animals were wormed thoroughly. After the worming, the control animals and those receiving the posterior lobe extract ap-

peared to recover quickly, but the animal receiving the anterior lobe extract in each of the remaining four litters seemed unable to overcome the results of the parasitic invasion. On the sixty-fifth day, because of the extremely weakened condition of the animal receiving the anterior lobe extract, it became necessary to kill another entire litter. On the eighty-third day, the animals being injected with anterior lobe extract of two more litters were in such a bad condition that both entire litters were killed and examined. Just subsequent to this the three remaining animals developed spasms—apparently worm fits, and it was felt necessary in spite of the weakened condition of the animal receiving anterior lobe extract, to worm them. On the ninety-ninth day, the animal being injected with the extract of the anterior lobe, of the last litter died and thus terminated the experimentation.

The results obtained in the second series of experiments were practically constant for the dogs receiving the same type of medication. In weight gain, for the first eight weeks, there was very little regular variation in the weight curves. Beginning about this time a constant variation began to be perceptible. While the curves for the control animals of the remaining litters remained a practically straight line, there began to be a slight rise in the curves for the animals receiving posterior lobe injections, with a coincident marked and constant decrease in the curves for those receiving anterior lobe extract. So regular were these variations within the different litters, that the curves for either litter would almost be descriptive of those for any

other litter. (See fig. 1.) A remarkable feature of the weight changes of the different animals is the contrast between the regularity of occurrence in the injection experiments, and the complete lack of regularity in the feeding experiments.

In the injection experiments some decided changes in external characteristics were likewise noted. While there was no noticeable difference in the external genitalia, as remarked by Cushing (1912), Goetsch (1916) and Beck (1912), there were differences in other external appearances coinciding in large part with their findings. The animals on anterior lobe extract had longer, coarser, drier coats. While they were, on the whole, more somnolent, they were at the same time bad-tempered when aroused, hyperesthetic to pain stimuli, and in the later stages they developed frequent and progressively pronounced epileptiform seizures. On the other hand, the animals on posterior lobe medication had a shorter, softer coat, were more active, less sensitive to pain, were even-tempered and affectionate, and their tape-worm fits were considerably lighter than even those of the control animals. These findings are almost directly opposite to those reported by Goetsch. The animals receiving anterior lobe medication showed a marked diuresis for a short time after injection, while if a variation in the frequency of micturition or the volume of urinary output was present in the other animals, it was not great enough to attract attention. This is not greatly at variance with the findings of Hammett, who observed that when the posterior lobe extract was administered subcutane-



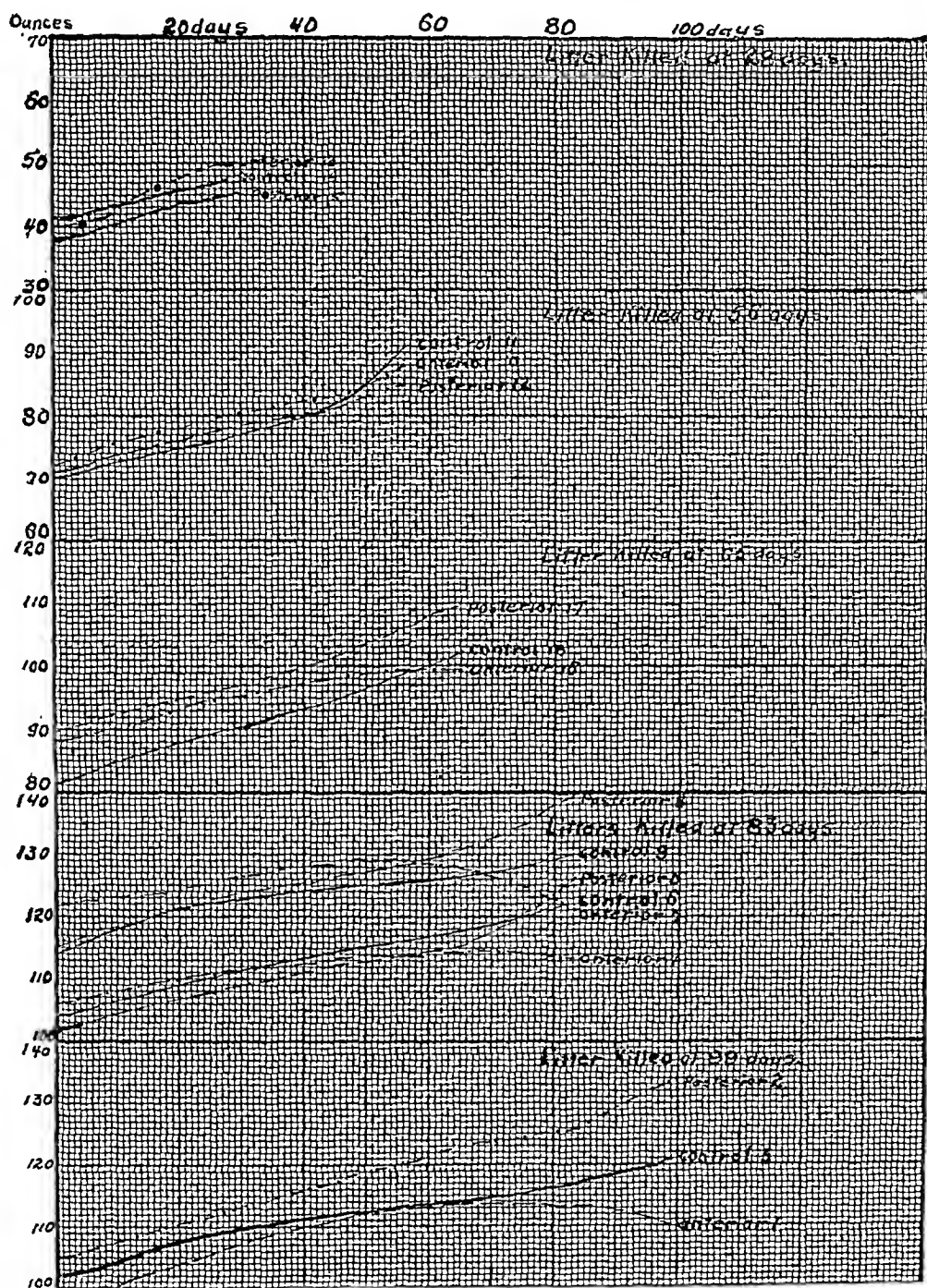


FIG. 1



ously it was apt to have an antidiuretic effect. It does, however, disagree with the findings of Motzfeldt (1917) who obtained an anti-diuretic effect from the administration of the extract of the anterior lobe.

The examination of the short bones, i.e., the vertebrae, was productive of only negative findings, but the tibiae yielded some marked variations. In the case of the animals receiving anterior lobe extracts, the tibiae were notably larger and showed greatly delayed epiphyseal closure as contrasted with the controls, while the animals on posterior lobe medication had smaller tibiae, with a more advanced stage of calcification. This, again, is in decided contrast to the results from the feeding experiments, where no regular differences could be noted.

It has been noted during the course of the experiment that in the injection experiments, there was an apparent increase in height in the animals receiving the anterior lobe extract. In order to check this, it was decided to work out a ratio between long bone and short bone development. For this purpose, two measurements were made of each dog, immediately after he was killed. One measurement, which was designated the short-bone component, was taken from the crest on the medial border of the scapula to the posterior superior iliac spine when the animal was laid on its side with the legs extended at right angles to the long axis of the vertebral column. This became, then, a coefficient for the size of the more constant short bones, the vertebrae. The other, or long bone component, was measured from the sole of the pad of the forefoot to the eminence on the

medial border of the scapula, while the animal was in the same position. For each animal the length component was then divided by that for the height and the ensuing figure carried to three decimals. With this resultant as the first component and 1000 (representing the height), as the second, a constantly comparable ratio resulted. (See Table I). From the table thus evolved it will be noted that the long bone development is constantly and progressively greater in the animals receiving anterior lobe extract, intermediate in the controls, and smaller in the animals on posterior lobe medication. This would seem to be in accord with the current views on the causes of gigantism and dwarfism. Again, it is in decided contrast to the results from the feeding experiments where no regular variations in height as opposed to length could be demonstrated.

The examination of the glands from the various animals elicited only minor differences, and those not of fixed character within the different types of medication. The gross examination of all of the glands was negative. The microscopic examination showed no mensurable change in the size, number, arrangement or nuclei of the secreting cells or colloid material of either lobe of the hypophysis or of the thyroid or parathyroids. The gonads, pancreas, thymus and pineal were not examined microscopically.

Bandler (1920) believed that the difference in growth and development in the respective sexes was largely due to the effect of the sex glands on the pituitary. An increase in the secretion of the anterior lobe in either sex caused a large bony growth, coarser

TABLE I

Animal	L-component		H-component		Time killed
No. 10 (anterior)	880	to	1000		56 days
No. 11 (control)	820	to	1000		56 days
No. 12 (posterior)	875	to	1000		56 days
*	*	*	*	*	*
No. 13 (anterior)	No examination of bones made on this litter.				
No. 14 (control)					
No. 15 (posterior)					
*	*	*	*	*	*
No. 16 (anterior)	880	to	1000		65 days
No. 18 (control)	870	to	1000		65 days
No. 17 (posterior)	820	to	1000		65 days
*	*	*	*	*	*
No. 4 (anterior)	890	to	1000		83 days
No. 6 (control)	870	to	1000		83 days
No. 5 (posterior)	820	to	1000		83 days
*	*	*	*	*	*
No. 7 (anterior)	895	to	1000		83 days
No. 8 (control)	870	to	1000		83 days
No. 8 (posterior)	825	to	1000		83 days
*	*	*	*	*	*
No. 1 (anterior)	895	to	1000		99 days
No. 3 (control)	875	to	1000		99 days
No. 2 (posterior)	825	to	1000		99 days

and heavier hair and the development of the masculine type of secondary sex characteristics. His investigations revealed the exactly opposite effect from an increase in secretion of the posterior lobe. He believes that marked hypersecretion of the posterior lobe causes acromegaly, as well as an abnormal accumulation of fat, particularly shoulder and girdle deposits. These findings agree in large part with those of Englebach and Tierney (1922). My own investigations would lead to conclusions in accord with these except that it would seem that changes in the bony skeleton would follow oversecretion of the anterior rather than the posterior lobe. It is a little difficult to

follow Bandler's conclusions, in that, although he attributes acromegaly to oversecretion of the posterior lobe, he at the same time finds the increase in secretion in the anterior lobe responsible for stimulation of bony growth. My own animals receiving anterior lobe extract did show a considerable increase in length and size of long bones with a coincident longer and coarser hair development. The posteriors showed almost the direct reverse.

Bandler speaks of polyuria in his animals on posterior lobe extract. Such I did not find to be the case. On the other hand in my animals receiving anterior lobe extract immediately after injection I could easily note a decided

increase in both frequency and quantity or urinary output. If there was any variation in this respect between my animals receiving the extract of the posterior lobe and the control animals it could not be noticed.

Crowe, Cushing and Homans (1910) found that repeated subcutaneous injections of the sterile extracts of posterior lobe led to emaciation. My own results tended rather to the opposite direction. I noticed a marked emaciation in the animals receiving anterior lobe injections with the opposite effect in those on posterior lobe. It is possible that a somewhat larger dosage may have so stimulated metabolic processes in my animals that the end result was emaciation. It is likewise possible that the wormy condition of my dogs was sufficiently marked to completely offset the effects of the medication.

However, in accord with P. E. Smith (1926) I am inclined to believe that the discrepancy in results so frequently noticed in endocrine experiments is probably due to the different methods of preparation used by the various manufacturers of the commercial products.

Summarizing—the feeding of pituitary preparations produced no observable changes. Injections of the posterior lobe extracts produced plumper, better proportioned and better-natured animals with soft, silky coats and an increase in epiphyseal calcification of long bones. Injection of the anterior lobe extract produced the reverse—emaciation, coarse, ragged coats, the “gigantic” type of skeletal development, bad-tempered animals, and a markedly delayed epiphyseal closure. In neither case was there a sufficiently marked change in the various endocrine glands to be susceptible of classification. The discrepancies found between this series of investigations and those of numerous other workers probably bears out P. E. Smith’s claim regarding the wide variation in methods of preparation of the commercial endocrine products.

I am greatly indebted to Dr. J. A. Badertscher of the Department of Anatomy of Indiana University for his kindly advice and guidance in a major portion of the experimental work involved and to Dr. G. Carl Huber of the Department of Anatomy, University of Michigan for his oversight and criticism of the manuscript.

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# The Alimentary Canal of the Medical Student, Radiographic Studies\*

BY T. WINGATE TODD, *Cleveland, Ohio*

THE emotions which express themselves through the alimentary tract have not yet been thoroughly studied. Some slight attention was given them during the later part of the Great War when we discovered many men who had literally no stomach for fighting. Further, insufficient attention has been paid to the mechanism and appearances of the normal tract, and we need to revise the technique of our routine examinations. There is nowadays, for example, no lack of power in our X-ray apparatus causing us to demand a starved stomach and purged bowel to enable us to see through a patient.

The willing co-operation of the medical students provides us with: first a layman unused to and somewhat apprehensive of all the strange and unknown experiences to which he is to become accustomed: and secondly a medical "man" perfectly attuned to all the sounds, sights and smells which are inseparable from a medical education. Further, both these phases occur in the same individual and can therefore be directly compared. The emo-

tions which are reflected in the alimentary tract are not conscious ones. The lack of tone in the Freshman's stomach, the stagnation in his duodenum, and the spasm of my own bowel the first time I underwent a long and possibly dangerous X-ray exposure cannot be influenced by any control on the part of the individual.

The movements of stomach and bowels may or may not be directly related to the passage onward of the contents which "seep" along whether peristalsis be present or not. In the small bowel the peristaltic wave changes its speed under different circumstances and is exceedingly slow in that part of the small bowel near its opening into the large bowel when the latter is spastic. The large bowel, contrary to what most of us have thought, presents precisely the same peristaltic wave as the stomach but with only half the speed of the stomachic peristalsis.

Apparently the stomach must be filled to a certain amount before it will empty even if vigorous peristalsis is present. The student stomach practically empties within  $1\frac{1}{2}$  to 2 hours. It will rapidly lose tone and possibly fill with gastric juice by the mere suggestion of food.

\*Abstract of address presented to the College of Physicians, Cleveland, Ohio, February, 1927.

*Summary*

1. The study of the normal alimentary tract in health of young male students affords a criterion for observation of pathological conditions.

2. All parts of the tract are exceedingly sensitive to emotional or nervous conditions. These influence different parts of the tract in divers directions. The stomach becomes atonic in outline though not in movement or in emptying time. The duodenum shows pseudostasis. The transverse colon exhibits a spasm which may absolutely inhibit the onward passage of contents.

3. The sites of cardia and pylorus are affected in similar manner though not so greatly as are the positions of

the greater curvature in the pyloric vestibule and gastric tube.

4. The normal position of the small intestine in the living, whether upright or horizontal, is in the lower abdomen and true pelvis: its disposition is in ladder coils.

5. Peristalsis in the lower ileum may be exceedingly slow in spasm of the transverse colon, one wave taking half an hour to complete its cycle.

6. The proximal colon (caecum, ascending colon, transverse colon) exhibits a peristaltic wave like those of the stomach and small intestine. Its rate of progress in the transverse colon is about half that of stomachic peristalsis.

# Transfusion in Preoperative and Post Operative Conditions With Anemia

By D. D. STOFER, A.B., M.D., F.A.C.P., *Kansas City, Missouri*

**I**MPROVED methods of Blood Transfusion within the past 10 or 15 years accompanied by a more thorough knowledge of blood grouping and cross-agglutination tests have made the transfusion of blood a considerably safer procedure than it was previously. Former hazards, such as sudden death and reactions of various types including chills, nausea and vomiting, high fever, etc., have been reduced to a minimum so that fear of these does not contraindicate the procedure in any way. The first transfusion upon a human being appears to have been done in France by Jean Denys of Montpellier, physician to Louis XIV on July 15, 1667. Richard Lower and a group of English experimenters had been performing transfusions on animals previous to this time and were waiting a suitable opportunity to transfuse a human being. Owing to the bad results obtained by using animal blood in human beings the procedure was abandoned for over a hundred years. In England, James Blundell, the obstetrician, reported a successful transfusion of a patient with human blood in 1824 using a special syringe he devised for this purpose. His prophecy made then that transfusion by the syringe is a very feasible and useful operation and after

undergoing the usual ordeal of neglect, opposition and ridicule will be admitted into practice—should place him in our memory for the accuracy of his prophecy.

The method of choice in the series of cases reported in this paper is the Lindeman direct syringe method. Blood grouping has been done merely for the sake of finding donors of the same group or of a universal group either by Brem or Moss classification to be cross agglutinated with the recipient's serum and corpuscles. At no time has a donor been chosen from a universal group or of the same group and used without first being cross agglutinated both as to cells and serum of each. Also, if the slightest agglutination is observed in either of the cross agglutination tests done microscopically, the blood has not been used. By safeguarding one's self by careful cross agglutination tests one need not fear serious results. Other safeguards such as cross agglutinating the blood after one transfusion before choosing a donor for a second transfusion on the same recipient; not using the same donor on the same recipient the second time; and careful inquiry into any history of allergic phenomena, prevent reactions to a considerable degree. In only one instance have I used the same

donor the second time, on the same recipient and this was in a case of extreme emergency where the patient's brother had to be used because of lack of time in which to find another donor. This case will be discussed later in this paper.

Owing to the fact that various subgroups of blood exist and also that people of the same group or of a universal group cause marked agglutination to appear in the cross matching of the bloods it is very unwise and disastrous at times to depend upon grouping alone unless the emergency is such, as it undoubtedly is in some cases, to warrant the use of a universal donor or donor of the same group. The natural cause of death is better explained than one following any mechanical procedure.

In all cases transfused within the past six years it has been the policy to introduce ten c.c. of blood into the vein of the donor and then wait for two or three minutes before proceeding. An accurate check of the pulse at the beginning and at the end of this time is taken. If the patient complains of any type of peculiar feeling or the pulse is raised very much, a longer period of time is taken before proceeding. The Lindeman multiple syringe and canula method has a distinct advantage in this respect since the transfusion may be stopped or started at will without fear of changing the blood to be given or having the experience of any clotting in or sticking of the apparatus.

Only in a very few instances have two donors been used on the same recipient at one transfusion. It is best to use but one donor and repeat the

transfusion if necessary at some later hour and then only after a careful cross matching of the bloods of donor against donor and donors against recipient has been done. By taking the time to perform these simple tests one may save the patient a disastrous result or a severe reaction which in itself is extremely unpleasant to both the patient and the operator.

The gradual loss of blood over a period of weeks, months, or years, reducing an individual to an anemic condition, weakness and ill feeling does not cause the serious results that the sudden loss of blood produces. Gradual loss of blood may have serious end results, still the patient has a better opportunity to adjust himself to the condition, than in the case of sudden loss of blood in large quantities. Sudden loss produces shock to such a degree that death may occur very rapidly because of the sudden collapse in the heart and blood vessels. Volume of blood is the important factor, and when reduced almost instantly, as in some cases, does not allow sufficient time for adjustment to the condition. Some of the volume can be replaced by intravenous saline or glucose, but both of these solutions are lost very rapidly, and neither has the properties to increase clotting time and thereby stop bleeding at the point where hemorrhage is taking place. After a patient bleeds to a certain stage, he seems to lose all properties of clotting. Whole blood seems to fulfill the need of shortening clotting time, building up volume, and all around adjustment of the blood system better than any other substance used to date. Results are almost magical as well as extremely



gratifying in the great majority of extreme and severe hemorrhage cases if done early enough.

Some physicians believe that hemorrhage will be increased if a transfusion is resorted to, to build up blood volume immediately after loss, but such is not the case in my series of cases. Blood when given shortens the clotting time instantly as has been proven in operative procedures where transfusion has immediately preceded the operation. A small amount of blood allowed to run into a small gall bladder spoon permitted of the same being inverted in two to two and one-half minutes with complete clotting whereas blood taken before transfusion would not clot to this extent in twelve to eighteen minutes. It has also been shown that very low blood pressure is not materially raised, especially in the presence of large blood loss and the shortening of the coagulation time that results is greatly to be desired. Cases with marked jaundice in which longer than normal clotting time is practically always present have been prepared for operation by giving a small transfusion beforehand and the method of testing clotting time as mentioned with a small gall stone spoon has been used to determine this factor before and during operation. The clotting time is unquestionably shortened after transfusion.

A very interesting feature observed in a large number of cases transfused where the loss of blood has been quite profuse—is the pulse rate. This deserves mentioning because of the fact that the writer has observed a pulse rate of 172 reduced to 116 in eight minutes after starting a transfusion of

900 c.c. of blood. In practically all cases where a very rapid pulse has been encountered the rate has been reduced very markedly. Later the pulse may rise again slightly if enough blood is not given to reproduce a fair blood volume, but usually keeps on decreasing to within normal limits if the original cause of hemorrhage does not play too important a factor.

Reducing reactions of any consequence to a small percentage, in cases in which the surgeon has to carry out a mechanical procedure immediately following the transfusion certainly allows him a better opportunity to do his work more carefully, thoroughly, and with far less danger to the patient. I believe that more anemic patients should be transfused before an operative procedure is resorted to, especially in acute hemorrhage cases and in cases of chronic sepsis of the type that produces secondary anemia of a marked degree, or chronic cases of bleeding from various surfaces such as the bladder, kidneys, and intestinal tract. Certainly, the surgeon should consider a transfusion as a great aid in these cases if his operative mortality will be reduced. If the patient is built back to within normal limits of blood volume he can better undergo the more serious types of operation.

The term, "Reactions of no consequence", is used in this series of cases to mean that a slight elevation of temperature of 99 to 101 degrees, such as would be encountered in almost any operative procedure, or a feeling of malaise for several hours does not constitute a reaction in the strict sense. Cases in which chills have been produced with pains in the back, down the

legs, severe headache, and sometimes nausea or vomiting accompanied by a marked rise in temperature illustrate a reaction of consequence. If the surgeon who is to operate the case after transfusion can be convinced that a reaction will not take place in more than one out of ten to twenty cases, surely he realizes his chances of relieving certain conditions, where excessive bleeding has taken place, are better if operated on at once than if he allowed the patient to start bleeding again some little time after the transfusion. In other words he can operate immediately after the transfusion.

The preoperative sudden hemorrhage conditions with which this paper deals are ruptured ectopic pregnancy, hemorrhage from a gastric or duodenal ulcer, severe hemorrhage in miscarriages or septic abortions, perforation of intestine (caused by accidental trauma to abdomen), ruptured spleen, hydatid mole and varices of esophagus from cirrhosis of liver. The preoperative gradual hemorrhage cases are ulcerative colitis, hemorrhage from uterus due to fibroids, polyps and endometritis, following abortion or miscarriage and Hunner ulcer of the bladder.

Postoperative sudden hemorrhage conditions are: uncontrolled hemorrhage following tonsillectomy, post partum hemorrhage, hemorrhage following gastroenterostomy, placental detachment in utero-prepartum and ruptured uterus during curettment. Postoperative conditions with gradual loss of blood which were transfused were: secondary anemia following empyema and rib resection, mastoiditis, miscarriages, and cases of osteomyeli-

tis. Several cases of some of each of the above named have been transfused but for the sake of brevity but one case of the more marked conditions will be given in this series.

*Case I.* Female, age 27. Intra-abdominal hemorrhage from ectopic pregnancy. When first seen by surgeon on Oct. 24, '26, patient was in a state of collapse and complaining of numb feeling all over her body as well as extreme weakness. Marked air hunger. Pulse 162, R. B. C. 1,780,000, W. B. C. 13,400, and hemoglobin 35%. 700 c.c. of blood given, pulse reduced to 108. Color of patient considerably improved at time of transfusion. Surgeon waited for two hours to see if any reaction would take place. There was no rise in temperature or chill. Abdomen opened. Ruptured ectopic pregnancy found and removed. Patient made uneventful recovery and left the hospital on the 12th day. Highest temperature posttransfusional and postoperative was 102.4 degrees.

*Case II.* Female, age 61. Seen November 18, 1922 at 12:30 a. m. About one-half hour before seeing patient she began vomiting bright red blood and passing blood in her stools. She was in complete shock. R. B. C. 1,220,000, W. B. C. 16,800, and hemoglobin 30%. She was sent to the hospital and transfused, 600 c.c. of blood given. Transfusion repeated in eight hours. Pulse reduced from 174 to 120. Abdomen opened. Ulcer excised by cauterization method. Made uneventful recovery. No reaction from transfusion. Highest temperature after operation and transfusion was 102.8 degrees.

*Case III.* Female, age 31. Ambulance case to the hospital March 14, 1921. Had abortion performed two weeks previous to admission. Bleeding from uterus constantly and very profusely for two days. Pulse not obtainable at wrist. Pulse over heart 166. Extremely pale and ashen in color. R. B. C. 1,180,000 and hemoglobin 30%. Intravenous saline containing one-half c.c. adrenalin given. Chill following this. Blood trans-

fusion 1,200 c.c. given using two donors. Temperature on admission 103.6 degrees. No reaction from transfusion. Uterus emptied immediately after transfusion. Uneventful recovery.

*Case IV.* Male, age 27. Brought into hospital April 7, 1921, following automobile accident. Was in state of collapse. Diagnosis made of perforated intestine with severe hemorrhage into abdomen. Blood transfusion, 920 c.c. blood given. Pulse reduced from 162 to 130. Perforation of intestine found with large amount of blood in abdominal cavity. Temperature following operation and transfusion was 102.6 degrees. Three days later wound broke wide open. Sutured. One week later patient began having severe pain in left side of abdomen with marked increase in pulse and temperature. Abdomen opened and volvulus found. Patient developed ether pneumonia following operation. Another transfusion of 640 c.c. was given because of his anemic condition at this time. Had rise of temperature to 104.8 degrees with slight chill. Went on to complete recovery in three weeks.

*Case V.* Female, age 7. Seen March 6, 1921. While coasting on a sled she ran into a park bench, left side of body striking bench with considerable force. Patient in shock. Abdomen distended. Blood transfusion 560 c.c. of blood given. No reaction. Operated one hour after and ruptured spleen removed. Highest temperature after transfusion and operation 103.4 degrees. Uneventful recovery.

*Case VI.* Female, age 26. Seen July 15, 1925. Had been bleeding profusely from uterus for three days. Condition fair, Pulse 144. R. B. C. 2,120,000, and hemoglobin 45%. Transfused, 650 c.c. of blood given. Pulse reduced to 110. Two and one-half hours after transfusion hysterectomy was done. This case proved to be a hydatid mole. Highest temperature 102.6 degrees. No reaction from transfusion.

*Case VII.* Male, 25 years of age. First seen in hospital April 1, 1921. Vomiting

large quantities of blood bright red and dark. In state of collapse and very pale. 580 c.c. of blood given. No reaction. Six and one-half hours later 710 c.c. of blood given. Had chill lasting 20 minutes following second transfusion. On following morning abdomen was explored and cirrhosis of liver found. Omentopexy was done. Patient recovered sufficiently in one month to leave the hospital in fair condition.

*Case VIII.* Female, age 25. First observed October 12, 1926. Bleeding from uterus constantly for one and one-half years. R. B. C. 2,120,000 and hemoglobin 40%. Transfusion 510 c.c. Bleeding did not stop entirely although decreased. Transfused again January 1, 1927, 600 c.c. of blood given. No reaction. Highest temperature 99.6 degrees. On following day D. & C. was done by surgeon. Radium used in uterus. Patient in good condition to date.

*Case IX.* Male, age 65. First seen February 20, 1927. Bleeding from bladder off and on for past fifteen years. Practically constantly for past three months. Hemoglobin 24%. The surgeon after cystoscopy made diagnosis of Hunner ulcer of bladder. Transfusion 690 c.c. of blood given. No reaction. Highest temperature 100.4 degrees following this. On March 1, 1927 620 c.c. of blood was given. No reaction. Temperature 100.2 degrees. Operated March 8. Patient in excellent condition to present time.

*Case X.* Female, age 31. Seen February 21, 1925. Following tonsillectomy had severe hemorrhage from throat during the day. Was given salt solution in large quantities without result. At 8:00 p. m. she became unconscious and pulseless. 580 c.c. of blood given one hour after this with result that patient became conscious with the finishing of transfusion. No reaction. On July 19, 1926 at eight and one-half months pregnancy this patient had a detached placenta in utero with marked evidence of severe hemorrhage. Surgeon performed caesarean section and upon finishing operation patient was transfused 560 c.c. of blood be-

ing given. Due to extreme emergency the same donor (her brother) was used in this case as on the first transfusion, one year and four months previously. Patient at this time had chill lasting about twenty-five minutes. No marked febrile reaction with this. Highest temperature being 102.8 degrees. She went on to complete recovery.

Patients with hemoglobin of 20 or below have been known to be successfully operated upon as shown by Baldwin. Lahey in his recent article on preoperative preparation of patients states that "No longer may one defend his position when operating on a poor risk, anemic patient, who has not had a blood transfusion previous to operation." The trend of the busy surgeon today is to realize this fact in its strictest sense because he knows from past experience that his mortality is unquestionably decreased in severe hemorrhage cases if transfusion is done previous to or immediately following his operative procedure. Also in secondary anemias of a more or less chronic nature as in some of the cases illustrated the patient has been made a good operative risk by transfusion.

Stoll in his recent article reports 100 cases done by his modification of the Lindeman method in which he works alone in doing the transfusion with a reaction in eight out of 100 cases. Last summer I had the opportunity of timing him while transfusing by this method and the shortest time that the blood was out of the body was one and one-fourth minutes and the longest time one and three-fourths minutes. The average length of time in the Lindeman method should not be more than 12 to 18 seconds from the time that the blood is started into the

syringe until it has been entirely introduced into the recipient's vein.

In shock it is now generally believed that the symptoms are due to a universal capillary dilatation which results in so much of the blood remaining in the capillary beds that the return flow to the heart is not adequate and the arterial blood pressure becomes very low. Apparently the individual bleeds into the capillary beds and not into his veins as was formerly thought. As a result the tissues suffer from lack of oxygen, which in turn leads to still further dilatation of the capillaries and in the more advanced stages to increased permeability of the vessel walls, so that a loss of plasma occurs, thus aggravating the circulatory failure. Transfusion if performed early restores the circulation and corrects the serious oxygen lack to the tissues. It is not of much value when shock has existed for several hours and the patient is practically moribund. If a lengthy and serious operation is to be performed in which shock is likely to take place it would be advisable to have the bloods cross agglutinated beforehand in order to lose the least time possible in performing the transfusion.

The contraindications of transfusion preoperative or postoperative are but very few—being acute cardiac conditions such as fresh vegetations on the heart valves or acute cardiac dilatation and certainly if surgery were indicated with these complications it would have to be postponed anyhow.

### *Summary*

Careful checking of the recipient's blood with that of the donor is absolutely essential for safety. The blood

should always be re-cross agglutinated after each transfusion if another is to be done. Consequential reactions of the type described which occur in approximately five to ten percent of the cases should not be a contraindication for transfusion.

The indications and limitations for preoperative and postoperative transfusions should be better understood

and advantage taken of the same more often.

Transfusion is the most successful means of combating severe hemorrhage or shock yet devised both preoperative and postoperative.

In chronic secondary anemic patients, transfusion undoubtedly makes the patient a better operative risk and its use may be life saving.

# The Laboratory Service in Civilian Hospitals

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## PART I

AS indicated by the title, this paper will deal with conditions obtaining in civilian hospitals for the physically ill, where they concern the laboratory service, though much that will be said might have application to the military service and to the service of mental hospitals.

Comparing the major services of a hospital—medical, surgical and laboratory,—we find a similarity which is useful for our purposes. Each major service has its acute cases, which demand short-time, intensive attention and its subacute or chronic cases, which demand prolonged, extensive attention.

In the first type of case, the physician or the surgeon is accustomed to request this or that procedure as he is guided by the indications in the case. One can scarcely condemn this practice where an emergency is concerned or where the diagnosis is clear or where the laboratory physician is little better than a technician. But in hospitals where the laboratory is in charge of a worker with clinical sense and experience, a consultation with the laboratory service may save a mistake in diagnosis—though the diagnosis was previously clear—and no element of time may be added to complicate the existent emergency.

A case in point is indicated:

*E. L.*, female, white, 20, school girl, was admitted with a diagnosis of acute appendicitis. The white blood count was 22,800 with 89% polys. The urine showed a trace of albumin and sugar, an occasional pus cell, three plus red cells (patient not menstruating), two plus renal tubule cells, and acetone.

Operation revealed a normal appendix and no abdominal pathology, but the right kidney was thought to be enlarged. Following operation the white blood count was still 20,000 and repeated urine examinations showed a definite acute nephritis with low volume output. Blood culture showed a gram-positive coccus and a gram-negative bacillus which were apparently of low virulence as the clinical course of the disease demonstrated.

Catheterization of the ureters revealed blood and pus from both kidneys and the left one showed bacteria in the urine. Recovery was prompt and uneventful, under treatment for the kidney condition.

A second case in point is as follows:

*A. N. E.*, female, white, 53, housewife, was admitted with a diagnosis of orbital cellulitis. The course of the disease showed that the portal of entry was probably the throat, with extension to the nose and, later, to the orbital structures. Smear from the right

tonsil, which showed a small amount of exudate, revealed Vincent's organisms and cocci; the nares showing bacilli and cocci; the orbital exudate showed cocci. Smear and culture were negative for diphtheria. Culture from the nasal and orbital exudate showed a short-chained gram-positive coccus which was lytic for coagulated blood serum. This organism grew as a pure culture on primary incubation.

White cell count was 1200. This finding was so surprising that it was repeated at once using fresh diluting fluid; the finding was 200. To make certain of our fluid a "normal" person was taken; her count showed 12,800 (she had just had a cold bath). The patient's count was first done thirty minutes after the administration of streptococcus anti-toxin intravenously. Twelve hours later the white count was 2,600; red count 3,950,000; polys. 28%, large mononuclears 26%, small mononuclears 44%. Another intravenous injection (this time antistreptococcus serum, polyvalent) was given. Two hours later the white count was 3,000; twelve hours later it was 800 and twenty-four hours later it was 1600.

Treatment included transfusion in order to bring up the power of resistance of the body, but patient grew worse progressively. Outcome was fatal.

These two cases, one surgical and one medical, show how the laboratory can be of service in emergency cases, without increasing danger by adding to the time element involved. In one case, we had the diagnosis and treatment correctly given by the laboratory findings where the clinical signs had misled the surgeon. In the other

case, the laboratory findings showed a hopeless prognosis, at the same time indicating the only known form of treatment that might offer hope of a favorable outcome.

I have selected these two cases because the usual run of routine cases with the usual laboratory findings are well known to everyone. At the same time, I want to stimulate the clinician, whether he is physician or surgeon to call in the laboratory more frequently even in his so-called "clear" cases.

## PART II

The Laboratory can be of still greater service in the subacute and chronic case. It is not our intent to exalt one tool of the clinical armamentarium above any other. It is not our intent to attribute greater merit to laboratory service than that which it has earned. The laboratory is not a perfect tool! Its ability is far below the demands placed upon it by some of the clinical problems referred to it. But it does offer certain standards of measurement or of comparison which are of value! Human beings used to measure by the "hand" and weigh by the "stone". We now measure by the micron and weigh by the thousandth of a milligram. By so doing we have come near to understanding the structure of the physical universe and of that part of it which concerns us as clinicians, namely, the structures and functions of the human body and those of the agents which act upon it. That is the service of the laboratory; to measure and to weigh more finely, to offer standards for comparison, ultimately so fine that we can recognize beginning disease before it has developed so far that any

layman can recognize it and possibly even identify it.

In this type of laboratory service to the subacute, the chronic or the apparently normal person who goes to his family physician for periodic examination at definite intervals, certain conceptions are fundamental.

The first of these is the conception of *stimulus* and *response*. In medical parlance we call these *etiology* and *symptom* or *physical sign*. It is absolutely essential, at every step in the analysis of a clinical problem, to keep this distinction between etiology and symptom (or sign) clearly in mind. The clinical tool for the discovery of etiology is the family and past history; for the discovery of symptoms, the personal history; for the uncovering of physical signs, the physical examination. The laboratory adds to the physical signs and to the etiology. Chemical studies of blood and urine, the routine tests of blood and urine, gastric analysis, spinal fluid studies are merely massing up or adding to the symptoms and physical signs already known to the clinician. They are of value in giving a more complete picture of the case and in guiding symptomatic treatment but they prove dangerous if they focus the attention of the clinician on symptoms to the exclusion of etiology. I believe that this point is worth mentioning because it is a really practical danger and not an imaginary one. The failure on the part of the clinician to make the distinction between etiology and physical sign, to the exclusion of etiology, is apparent every day that we practice medicine.

The laboratory is searching for etiology when it concerns itself with

bacteria. How often that is we all know. As compared with the number of procedures done in clinical laboratories for the discovery of further physical signs, the number of procedures for the discovery of etiology is insignificant. I will not say that the attention of the laboratory should be focussed on etiology but my opinion is that the laboratory could make its greatest contribution to clinical medicine, if the clinician would demand more often that attention be paid to any bacteria found whether in the urine, the feces, the sputum or in any other of the excretions or exudates. Unfortunately the laboratory cannot follow its own tendency in this matter. The demand must come from the clinician, unless the clinician sees fit to take the laboratory physician into consultation, in which case the laboratory worker has an opportunity to make the desirable suggestion. Such investigations into etiology should include a study of the comparative virulence of the organisms found and should lead to suggestions as to therapy, whether treatment should aim to establish immunity by the use of sera (passive immunity) or by the use of vaccines (active immunity).

This leads us to consider another matter of vital importance from the laboratory standpoint, namely, the "portals of entry" of disease. This is a matter of fundamental importance in any clinical case, but our perspective is lost very often when looking at a case from the numerous angles which have to be considered by the clinician. The importance of the "portal of entry" stands out in its true perspective when the case is considered from the labor-



atory standpoint. From this standpoint we are not concerned so often with hereditary factors in etiology nor with trauma but we are concerned immediately with the mucous membranes, namely, with the respiratory tract, the gastro-intestinal tract and the genito-urinary tract. Excluding heredity and trauma, etiological agents affect the body through these three tracts. I am speaking of physical diseases. In the case of mental diseases, not due to physical disease, but due to environmental situations, of course the portal of entry is the sense organs, but we are not concerned with mental disease in this paper, nor with behavior problems such as delinquency, criminality, et cetera.

The upshot of these remarks is that the study of every clinical problem in the subacute, the chronic and preventative groups should involve a thorough study of the portals of entry. This means that the air we breathe, the food we eat and the care or lack of it that we take in matters of personal hygiene of the main portals of entry, should come under consideration in any adequate study of these classes of patients. Such studies are profitable both for the institution concerned and for the patient under observation. I might add that, in my opinion, no period of observation in such cases is complete or fair to the patient or the institution which does not include such a study.

With such attention, as I have indicated, directed to the portals of entry and to etiology we might expect to see the disappearance of such symptom complexes as "diabetes" and "essential hypertension," for example. There are

many others but let us consider only these two. Each consists of a set of symptoms, physical signs and laboratory findings none of which says a word about etiology or about the portal of entry. Hence each is shrouded in darkness. Though far from knowing how to cure, we are much nearer an understanding or comprehension of such diseases as syphilis and tuberculosis for in each of these diseases we have the etiological agent; we know how to look for and often how to find the portal of entry; we can determine with some assurance the organs involved and we can ascertain to an extent their functional pathology.

This leads to some remarks on the subject of *disease* in general. All disease involves structure or form and description is couched in words which have to do with structure, whether gross or microscopic. I am omitting for the moment abnormal chemical reactions demonstrated by stains, though these have to do ultimately with abnormal physical or chemical structure or form.

All disease involves function or activity. A tissue becomes overactive or underactive or at times one and at other times the other. We say that such a structure is hyperfunctional or hypofunctional or dysfunctional (hyperkinetic, hypokinetic or dyskinetic). Such a structure is over-sensitive, under-sensitive or of alternating sensitivity; it is over-responsive, under-responsive or of alternating responsivity.

The structural, the functional and the etiological are fundamental in any description of disease. If we would keep this in mind we would soon have a classification of all diseases which

would be simple, definite and unequivocal. Every disease would have an anatomical "surname", a functional "middle name" and an etiological "family name".

The last few paragraphs may seem to have little relation to my topic. The connection is this. In most of our acute cases we see, at first, hyperfunctional symptoms. The laboratory should be asked to look for irritants whether they are bacterial or otherwise. Later, we see dysfunctional symptoms as the patient's reserves begin to fail and, finally, we see hypofunctional symptoms where the body is failing to respond. What the laboratory can do and what it should be requested to do should be regulated largely by these considerations whether the case be acute or whether it be chronic.

Prognosis and treatment, I believe, can be based upon the same considerations. I hope to see the time when drug action will be taught under the fundamental captions mentioned: first, the organ affected; second, the sort of effect produced, proceeding from irritation or stimulation to paralysis or inhibition of function. But more important than this, I hope to see the bacterial poisons isolated and studied in the same way and finally, in treatment, we ought to study the reverse action of curative sera, conferring passive immunity, and of vaccines, conferring active immunity.

The following is an illustrative case:

P. M., female, white, 54, single housekeeper, was presented for study. She has a long history of gastro-intestinal trouble dating back for 25 years. She has made the rounds of the clinics

in several cities without relief. She complains of weakness, palpitation, feels as though she is going to die at times; a typical neurasthenic syndrome with certain psychasthenic features. She has distinct "air hunger". Her *basal metabolism* varies as follows: plus 872, plus 438, plus 272, plus 6, plus 68. Her *blood pressure* varies as follows: 170/100, 160/96, 174/90, 180/95, 146/88. Her weight is 110 pounds, which is 23% below normal for her age and height. *Urinalysis* showed 4 plus acid, one plus blood, 2 plus pus, 1 plus hyaline casts; later, three plus acid, rare pus cell, no indican; there was no fixation of specific gravity or of quantity (*Mosenthal*); *functional test* showed 60% in 2 hours, which is the lower limit of normality. In other words we were not dealing with a kidney lesion with resulting retention of metabolic poisons to account for the clinical symptoms.

We tried to multiply our symptoms on the side of a neurosis but without much result, as follows; the adrenalin test showed some evidence of unstable sympathetic nervous system with adrenal minus; the pituitrin test pointed to the thyroid plus with pituitary and sympathetic minus; the atropin test pointed to vagus minus; the pilocarpine test showed normal or diminished vagus irritability; thyroxin had no effect; sugar tolerance test showed overactive utilization of sugar (high tolerance) which points to overactivity in one or more of several locations. The ensemble shows a marked dysfunctional (dyskinetic) splanchnic nervous system. So far we have merely multiplied physical signs.

Our next attack was on the liver.

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would be simple, definite and unequivocal. Every disease would have an anatomical "surname", a functional "middle name" and an etiological "family name".

The last few paragraphs may seem to have little relation to my topic. The connection is this. In most of our acute cases we see, at first, hyperfunctional symptoms. The laboratory should be asked to look for irritants whether they are bacterial or otherwise. Later, we see dysfunctional symptoms as the patient's reserves begin to fail and, finally, we see hypofunctional symptoms where the body is failing to respond. What the laboratory can do and what it should be requested to do should be regulated largely by these considerations whether the case be acute or whether it be chronic.

Prognosis and treatment, I believe, can be based upon the same considerations. I hope to see the time when drug action will be taught under the fundamental captions mentioned: first, the organ affected; second, the sort of effect produced, proceeding from irritation or stimulation to paralysis or inhibition of function. But more important than this, I hope to see the bacterial poisons isolated and studied in the same way and finally, in treatment, we ought to study the reverse action of curative sera, conferring passive immunity, and of vaccines, conferring active immunity.

The following is an illustrative case:

P. M., female, white, 54, single housekeeper, was presented for study. She has a long history of gastro-intestinal trouble dating back for 25 years. She has made the rounds of the clinics

in several cities without relief. She complains of weakness, palpitation, feels as though she is going to die at times; a typical neurasthenic syndrome with certain psychasthenic features. She has distinct "air hunger". Her *basal metabolism* varies as follows: plus 872, plus 438, plus 272, plus 6, plus 68. Her *blood pressure* varies as follows: 170/100, 160/96, 174/90, 180/95, 146/88. Her weight is 110 pounds, which is 23% below normal for her age and height. *Urinalysis* showed 4 plus acid, one plus blood, 2 plus pus, 1 plus hyaline casts; later, three plus acid, rare pus cell, no indican; there was no fixation of specific gravity or of quantity (*Mosenthal*); *functional test* showed 60% in 2 hours, which is the lower limit of normality. In other words we were not dealing with a kidney lesion with resulting retention of metabolic poisons to account for the clinical symptoms.

We tried to multiply our symptoms on the side of a neurosis but without much result, as follows; the adrenalin test showed some evidence of unstable sympathetic nervous system with adrenal minus; the pituitrin test pointed to the thyroid plus with pituitary and sympathetic minus; the atropin test pointed to vagus minus; the pilocarpine test showed normal or diminished vagus irritability; thyroxin had no effect; sugar tolerance test showed overactive utilization of sugar (high tolerance) which points to overactivity in one or more of several locations. The ensemble shows a marked dysfunctional (dyskinetic) splanchnic nervous system. So far we have merely multiplied physical signs.

Our next attack was on the liver.

This was found to be underactive, 20% of the dye ("tetrachlor") remaining at the end of 15 minutes, 17% in one hour and 15 minutes, and 3% in two hours and fifteen minutes. This finding checked with the hemoclastic crisis test of Widal and Abrami (W. B. C. 8200, 8200, 8000). Here then we have an adequate source for the clinical picture. We appear to be dealing with a complicated intoxication due to failure of the de-toxicating power of the liver. But, having found the cause of our symptoms, we cannot pause because we know that the liver is never a *portal of entry* except by direct injury and by heredity. Neither exists in this case. The genito-urinary tract was ruled out. The respiratory tract was ruled out. The hemo-lymph system was ruled out except for a pair of old tonsils which the patient refuses to have removed. We are left, then, with our history of gastro-intestinal disorder of many years duration.

The examination of the stool reveals a foul, semi-solid specimen containing undigested fat and starch with 40% Gram positive bacilli and cocci. Here

we seem to have our etiology in a pathogenic gastro-intestinal flora.

Treatment indicated is to change the flora in order to prevent further damage, but prognosis is poor as to repair of damage already done and is doubtful as to our ability to maintain a normal flora, though some progress has been made in this direction with good clinical results, so far.

### *Conclusion*

I do not wish to extend this paper beyond reasonable length but I want to emphasize once more the importance of considering disease from the tripartite standpoint of the pathological structure, pathological function and etiology. Secondly, I want to emphasize the fundamental nature of the distinction between symptom and cause. Thirdly, I want to recall to your minds that the laboratory as now organized performs its chief service by multiplying physical signs for you. Fourthly, I want to bring a realization that the greatest future service of the laboratory will be in the field of etiology and of treatment.

## Editorial

### *THE COMING MEETING IN NEW ORLEANS*

At this time there is being shown an unusual degree of interest in the coming Clinical Meeting of the College in the city of New Orleans, during the week of March fifth; and the prospects of an unusually large gathering of Fellows and Associates seem certain. One hears from all sides anticipations or promises of attendance. No other meeting of the College has called forth so many expressions of eagerness and desire to attend as has this one; and for very good reasons. New Orleans has so much to offer of interest along so many diverse lines. The climatic change—the prospect of meeting an early spring on the shores of the Gulf, in the first week of March, is in itself a great inducement to the Northerner; and this alone will be sufficient to persuade some practitioners to drop their work for a week and seek a pleasant recreation in the real old South, where traces of southern history and manners still linger. And racial mystery and romance as well! New Orleans has a very individual atmosphere and flavor—almost that of a foreign city. A visit to it gives the same thrill of discovery and surprise as going abroad. It has not yet been fully Americanized. The city has been described as “a Parisian who came two centuries ago to the banks of the Mississippi, and

has never cared to return to her mother country.” Perhaps no other characterization of the Crescent City could be so apt as this one—the city of the French adventurers—of the Creole—of the Mardi Gras—the Old Ursuline Convent—memories of the old French Opera—the Creole balls—and the old restaurants—the old cemeteries—these reminders of its two centuries of history betray its Gallic origin and spirit. All of this story of the city’s past has been most charmingly told by Grace King in her book “New Orleans, The Place and the People,” of which the Macmillan Company put out a new edition in 1926. A native, herself, she tells the fascinating tale of New Orleans with love and sympathetic understanding of the city and its people, throughout the whole period of its history, from the early discoveries and exploration of the Mississippi river, through the colonization of Louisiana and the founding of New Orleans, the French immigration, the Spanish domination, the American purchase and control, the episodes of Lafitte and Jackson’s victory, antebellum days, the Civil War, down to the modern period of development. The interesting story is told in a charming personal manner as of a personal recollection, projected against a background of historical development, with here and there lurid gleams of early slave days, the buccaneers, old Creole times, the social

menace of the quadroon, duels under the oaks, and the savage superstitions of voodism still persistent. Not omitted are the great epidemics of cholera and yellow fever when year after year the specter of death lurked in the city. In 1853, out of a sixty thousand population, forty thousand were attacked and eleven thousand died of yellow fever. In 1854 and 1855 the fever returned with cholera with a death rate of seventy two and seventy three per thousand. Look up in your library the contemporary accounts of these epidemics in the medical journals of those years. Within our generation medicine has seen the conquest of these great plagues, and New Orleans happily will never again know the constant menace of death as experienced by its inhabitants during the first three quarters of last century. We strongly advise the reading of Grace King's book to any one planning to visit New Orleans. From no other single volume can so much of the soul of New Orleans be obtained. Its charming little illustrations will also indicate the architectural and historical bits one will wish to search out. With this book in hand delightful sallies of exploration into the *vieux carré* may be made from the headquarters hotel. And there are other attractions in these explorations of street and alley, old furniture, old ironwork, and other relics of Creole days may still be picked up, even an occasional book or two of interest. There are also the restaurants where characteristic Southern and Creole food is still served offering fine opportunities for gastronomic adventures. Advice from a native citizen is to this effect—"Take

your breakfasts in the hotel, but go to various of these characteristic restaurants for other meals." A complete exploration of city, the river front, the residential portions and the old cemeteries will occupy a large part of the time not taken up by the meetings, or all of it, according to how thoroughly one studies the city. Several days should, however, be added to the five days of the meeting, in order to do it well; and any one who can accomplish this will surely be well repaid for the extra time spent. In addition to Grace King's book, there has recently been published by Doran an "Impressions of Old New Orleans in Pictures" by Arnold Genthe, conveying artistically the charm and beauty of the remaining bits of the old city, and this we advise you to study before you go to New Orleans, and then, when you are there, to search out similar bits of architectural beauty in the old courts and alleys, in the lights and shadows of arch and balcony, stairway and ancient walls. If photography is one of your hobbies here is a rare opportunity to collect visual impressions of real pictorial value. Perhaps you have been told that New Orleans has been ruined artistically by its rapid modernization—that the old things are gone, the old buildings destroyed, the old French Opera House burned and other like discouraging things. Some of this unfortunately is true, but the work of destruction of the old and beautiful has been halted in time to save much that still makes New Orleans unique among our cities. In the *vieux carré* the spirit of the old Creole life may still be found if one looks for it. And

then if you do recapture it you will understand the soul of New Orleans in its significance to the rest of American cities—it was France transplanted to the wilderness of swamp, bayou and mighty river—France it remained through the Spanish domination—purchased by the United States, over a century of American ownership and transforming influence has not yet effaced its hereditary characters. New Orleans offers us still the charm of ancestral foreign manners and customs to a greater degree than any other city within the bounds of the United States. The great and menacing river upon, or perhaps we should say beneath, whose shores the city is built will be of especial interest to every visitor to the city. The second greatest port in the country, its docks constitute a wonderful water front of over twenty miles. There are said to be many interesting river excursions available. The shore of the Gulf, with its summer houses, bathing beaches and pine forests also offers other opportunities for pleasant recreation. We are saying so much about the attractions of New Orleans as a fascinating city that we are neglecting perhaps the medical side of the meeting. A glance at the program will convince the Fellows of the College that there has been prepared for them a notable set of lectures and addresses by well-known internists, and that these presentations will offer new aspects and phases of the problems connected with cancer, the anemias, tuberculosis, cardiac disease, epilepsy, abnormal metabolism, diabetes and the infectious diseases. These contributions have been logically arranged in groups in the pro-

gram and it is certain from the character of the men presenting these that all of the papers will be up-to-date vital presentations of the subjects chosen for these symposia. A definite effort has been made to make of the morning and evening sessions post-graduate courses in the best meaning of that somewhat overworked phrase. Instead of a confusing mixture of subjects each session will have a well-defined entity of subject and treatment, and in this respect it is hoped that the listeners will be able to carry away with them more clear concepts of the subject matter than is usually possible under the confused and hurried manner in which most so-called post graduate courses are conducted. Two especially notable features stand out on this program. Dr. Julius Bauer of Vienna will present the opening address of this meeting. He holds now the recognized position of being one of the foremost thinkers in internal medicine, and his views on constitutional pathology have made him perhaps the chief European proponent of the modern philosophy of medicine. His address and clinics will in themselves secure for this Clinical Week a degree of prestige not equalled in any of the previous meetings. We must again call attention to the clinics offered by the local profession. In them there will be presented an abundance of clinical material peculiar to the Gulf Region, and the visitors will have a wonderful opportunity of becoming acquainted with a variety of subtropical diseases at first hand. The opportunity to visit the Leper Colony is another medical opportunity not to be overlooked.



## Abstracts

*Antirachitic Effect of Skyshine.* By FREDERICK F. TISDALL and ALAN BROWN (American Journal of Diseases of Children, November, 1927, Volume 34, pp. 737-741).

The term skyshine is used to designate the sun's rays that are reflected from the sky and clouds in contradistinction to the rays received directly from the sun itself. An object placed on the sunny side of a street receives rays not only from the sun but also reflected rays from the sky. On the shady side of the street only the rays reflected from the sky (skyshine) are received. If the object is again placed on the sunny side of the street and if a long cylinder pointed directly at the sun is placed over the object, the rays from the sky are cut off by the walls of the cylinder, and only the rays directly from the sun pass along the inside of the cylinder to the object at the bottom. No previous studies of the antirachitic effect of skyshine have been recorded. In 1920, Dorno reported that when the sun is at its height in the sky, the reflected ultraviolet rays from the sky (skyshine) are 15 per cent greater in amount than the ultraviolet rays received from the sun directly. According to Dorno, then, if an object is placed on the shady side of the street with the sun at its height, the object will receive 15 per cent more ultraviolet radiation than if it is placed at the bottom of a cylinder which cuts off the skyshine and allows only the direct rays of the sun to fall on it. The authors carried out a series of experiments on rats to determine the antirachitic effect of skyshine. As a result of their investigation they conclude that the antirachitic effect of sunshine (reflected rays from sky and clouds) is approximately from one-half to two-thirds as great as that produced by what is ordinarily termed sunshine (rays

from the sun plus the reflected rays from the sky). Reddening of the skin by ultraviolet rays is not a suitable unit for the measurement of ultraviolet therapy. It should be regarded simply as an accompanying phenomenon which may or may not be a measurement of ultraviolet rays received.

*The Effects of Measured Amounts of Ultraviolet Radiation on the Blood Count of Normal Rabbits.* By MARY HARDY (American Journal of Hygiene, November, 1927, Volume VII, pp. 811-837).

The conclusions of this investigation are summarized as follows: Single radiations from a quart mercury arc, in doses from 12 to 48 lithopone units of ultraviolet energy, produce no change in the erythrocyte count in normal rabbits. Successive daily doses of 12 L. U. for eight days had no effect on the red count during the radiation period. After radiation was discontinued there was a slight rise which lasted for about a fortnight. The platelet count was increased by single doses of radiation, the rise varying directly with the amount of ultraviolet energy given. Successive daily doses increased the amount progressively, so that the extent and duration of the rise was greater than that following any single dose. The immediate effect, both with single and successive doses, was a short drop which was followed by the marked rise above normal. Successive small doses, of 12 L. U. for eight days, did not bring about any change in the white count. There was an initial drop in the lymphocytes, and, therefore, in the total count, within an hour after radiation, but the count was normal the next day. An initial drop in the lymphocytes is a constant reaction to all ultraviolet radiations given in single and in successive daily doses. Variation in the amount of radiation has little effect on the

extent of the drop, but the duration is directly proportional to the dose. After a massive single dose of 96 L. U., the lymphocytes remain below normal for several days. Ultraviolet rays, shorter than 300 m $\mu$ , produce an increase in lymphocytes, following an initial drop, provided the dose is not too great. The rise reaches a maximum two or three days after radiation. The maximum increase is probably caused by a specific amount of ultraviolet energy. Under the conditions of this experiment the optimum dose was about 24 lithopone units. Heavy radiations of the region of wave lengths shorter than 275 have no effect on the polymorphonuclears, but rays between 275 and 320 m $\mu$  produce a sharp rise in these cells which reaches a maximum in about five hours. The increase above normal lasts for several days, and is proportional to the energy of ultraviolet radiation in the region between 320 and 275 m $\mu$ . The changes in the blood cells observed in this investigation were in no case phenomenal. It must be pointed out, however, that the animals were all normal and living under ordinary conditions of food and environment. Animals kept in the dark, or having a low blood count to begin with, would probably respond more readily to radiation than would a normal rabbit. Since ultraviolet radiation has been used so extensively in the treatment of rickets, investigations have shown that irradiation of normal animals does not bring about an increase above normal in the blood calcium or phosphorus. It is interesting, therefore, to have found consistent changes in the blood count subsequent to radiation of normal individuals. Radiation of individuals with low counts might be expected to produce more striking effects. The fact that only a narrow range of ultraviolet intensity is capable of producing a lymphocytosis corresponds to observations on other biological phenomena where short exposures are found to be stimulating and larger ones depressing. It has already been noted (Pena and Clark, 1924) that the growth of fungi is stimulated by short exposures and depressed by large ones. Unpublished

work by O'Donnell has shown increased irritability of melanophores after a short exposure, with a maximum irritability for a certain definite dose. Stronger doses resulted in a decrease in irritability and eventually death. In the same way a definite amount of ultraviolet energy produces a lymphocytosis, but for larger exposures, the initial drop lasts for a number of days, giving a lymphopenia. This suggests that in the therapeutic use of ultraviolet radiation there may be an optimum dose and that greater doses may be useless or even harmful.

*Analysis of Morphological Blood Changes in Pernicious Anemia Following Administration of Liver.* By CHARLES H. WATKINS and HILDING BERGLUND (Proc. Soc. for Exper. Biology and Medicine, December, 1927, XXV, p. 206).

The introduction by Minot and Murphy of liver diet in the treatment of pernicious anemia has supplied experimental medicine with a hitherto unequalled method of studying blood formation. Three general types of anemia have been produced experimentally, secondary anemia due to hemorrhage, the aplastic anemia due to the destruction of the blood forming elements in the bone marrow and the hyperchromatic anemia produced by certain poisons. The fact which differentiates the condition in pernicious anemia from the types of anemia that have been experimentally produced, is that in pernicious anemia a blood is available which shows a low spontaneous regenerative activity and yet the bone marrow is not aplastic. Minot and his co-workers have shown that after about two months of the liver treatment, the morphological picture of pernicious anemia has returned to practically normal. Watkins and Berglund have made a detailed study of the morphological blood features in the case of a woman 52 years of age presenting the classical features of the disease. Before the liver diet (all liver given raw) the morphological picture was studied for 5 days. At the time the liver diet was started the total number of normoblasts per

cu. mm. of blood was 78. Immediately after the liver was started they increased rapidly so that by the 8th day the total number was 870 per cu. mm., after which there was a gradual decline until by the 16th day they had disappeared. The highest percentage for the normoblasts was 1015 on the 8th day. The reticulocyte curve began to rise 4 days after treatment was begun and reached its peak on the 15th day at which time the normoblasts had practically disappeared. The increase was 9,900 per cent on the 15th day. This represents the highest percentage increase of any of the formed elements. There was a slight secondary rise in the normoblast curve on the 13th day and a similar one occurred for the reticulocytes on the 23rd day. At first this was thought to be an individual variation, but it has since been seen in other cases. The total red count remained constant until the 6th day after the diet was started and then there was a marked increase up to the 18th day. From this time on the count rose more slowly up to normal. The increase in erythrocytes was about 410 per cent which was reached about 50 days after liver was started. Comparing these curves with the graphs of the reticulocytes, it will be found that at the time of the most rapid increase in the reticulocytes there is also the most rapid increase in total red cells. Although the reticulocytes offer a good means of estimating the regenerative activity of the

bone marrow, they do not represent the only method of erythrocyte production. Thus the total reticulocytes increase to slightly over 600,000 per cu. mm., while at the same time the total red cells increase from below 1,000,000 up to more than 3,000,000 cells per cu. mm. Therefore, many mature red cells are being released from the bone marrow along with the less mature reticulocytes. During the liver treatment the eosinophiles increased from 2 per cent to 48 per cent of the total number of leucocytes; the eosinophilia begins after the peak of reticulocytosis has been reached, and at the time the rapid increase in the red cells has diminished. Although the morphological blood picture returned to normal following the liver treatment, the so-called "pernicious anemia neutrophiles" remained. This was observed in other cases also. Whether this deviation from the normal will ultimately disappear has not been established, but it is of aid in the diagnosis of pernicious anemia after the blood picture has become essentially normal. The authors conclude that megaloblasts are not essential in the diagnosis of pernicious anemia. Liver diet causes a response in the circulating blood in the form of an appearance of normoblasts, reticulocytes, mature erythrocytes and eosinophiles in the order given. The progressively increasing eosinophilia may be an expression of an overdosage with liver.

## Reviews

*Diseases of the Mouth.* By STERLING V. MEAD, D.D.S., Professor of Oral Surgery and Diseases of the Mouth, Georgetown Dental School; Professor of Diseases of the Mouth, Georgetown Medical School; Oral Surgeon to Georgetown Hospital; Dental Surgeon to Providence Hospital; Consulting Oral Surgeon to Casualty Hospital; Consulting Dental and Oral Surgeon to Shady Rest Sanitarium; etc., Washington, D.C. 578 pages, 247 original illustrations in the text and 29 full page color plates. The C. V. Mosby Company, St. Louis, 1927. Price in cloth, \$10.00. .

The author states that the preparation of this work upon diseases of the mouth has been prompted by the conviction gained from the teaching of both dental and medical students and from a large consultant practice, of the constantly growing need for a more intimate co-operation between dentists and physicians in the effective handling of the intricate problems of oral sepsis and other affections of the mouth which, if not intelligently diagnosed and treated, may affect disastrously the general health of the patient seeking dental or medical relief. The volume has been written primarily as a textbook for dental and medical students, but the author hopes that it will also supply both dentists and physicians in the practice of their professions with the fundamental principles and practical knowledge necessary for their routine work in making a correct diagnosis of abnormalities within the mouth, and thus to permit them to give a correct prognosis, so that proper treatment may be applied more promptly and efficiently than in the past. In order to accomplish this the author presents a definite routine plan of procedure for the making of oral examinations, for the recording of the data so obtained, and

for the future care of the patient, whether he be referred from the physician to the dentist or from the dentist to the physician for subsequent treatment. For this purpose the author has aimed to give his own personal experiences and observations rather than to quote from the writings of others. The literature has also been carefully examined, and the important references upon the various subjects discussed are given at the end of each chapter. The book has been profusely illustrated with drawings, photographs and radiograms as the nearest approach to personal clinical observations and individual contact in the teaching clinic. There are 34 chapters, the first sixteen of which are concerned with dental material chiefly: oral examination, radiograms, diagnosis of pulp vitality, transillumination of teeth and gums, bacteriologic examination, disorders of enamel, dentin and cementum, dentition, abnormalities of the teeth, malocclusion, saliva, dental calculus and accretions upon the teeth, impacted and unerupted teeth, periodontal diseases, diseases of dental pulp, periapical diseases and pulpless teeth. The remaining chapters treat of infections of mouth, floor of mouth and neck, diseases of the blood, blood vessels and nerves involving the mouth, diseases of the lip, tongue, throat, salivary glands and ducts, maxillary sinus, congenital clefts of lip and palate, stomatitis, diseases of the mandibular joint and muscles of mastication, maxillary bones, tumors, cysts and relationship of oral sepsis to systemic disturbances. Many of the subjects are very superficially treated and its chief value would seem to be that of a large manual listing the various abnormal conditions without an adequate treatment of any one. The book is of much greater value to the dentist than to the physician because of this rather handbook method of superficial treatment. Likewise,

the many illustrations are chiefly of dental interest.

*Nasal Neurology, Headaches and Eye Disorders.* By GREENFIELD SLUDER, M.D., F.A.C.S., Clinical Professor and Director of the Department of Oto-Laryngology, Washington University School of Medicine, St. Louis. 428 pages, 167 illustrations including 2 color plates. The C. V. Mosby Co., St. Louis, Missouri, 1927. Price in cloth, \$11.50.

Since the appearance of his monograph, in 1918, dealing with headaches and eye disorders of nasal origin, the author has become constantly more impressed with the neurological side of rhinology. He has chosen the above title for the present volume with the special intention that it may attract the interest of neurologists, internists and ophthalmologists to a greater extent than the customary treatise on rhinology. Rhinology greatly needs this cooperation for two very definite reasons, namely, in order to secure clinical cooperation in obscure neurological cases and in order to obtain post-mortem material in which the life history of the individual is definitely known. Material for the study of the pathology involving these tissues is the most difficult of any to obtain, in fact, hitherto it has been impossible to obtain. In the chapter on Some Neurological Problems special emphasis has been laid upon the neurological side of rhinology and the special part played by the involuntary nervous system which is superficial in the nose and nowhere else in the body. Most of the recent clinical and experimental work on the involuntary system has been reviewed in this chapter with the hope of exciting ideas in the minds of others concerning the nose and the involuntary system. In the volume are also included material of a purely rhinological interest, an antrum technique heretofore not published, a chapter on orbital abscess and one on anterior ethmoidal neuralgia. There are ten chapters, distributed over the following divisions of the subject: the minute pathological anatomy by Jonathan Wright; the nose; vacuum frontal neuralgia; the syndrome of nasal ganglion neu-

rosis; hyperplastic sphenoiditis and its clinical relations to the environing nerves; some neurological problems in rhinology; surgery of the maxillary antrum; orbital abscess and case histories. Eighty-three pages are given to this last chapter. The book is clearly and concisely written, the illustrations are largely from drawings showing anatomical relations or operative procedures, and are very satisfactory for the purposes for which they are designed. The lack of pathological material upon this subject is reflected in the lack of illustrations concerned with the pathological basis. For that reason the discussion of the various clinical conditions appears somewhat empirical. The author recognizes this in the closing paragraphs entitled Afterthoughts. While believing that many cases of headache are caused by hyperplastic lesions of the post-ethmoidal-sphenoidal area, he does not hold that his lesion is the explanation of all cases. The whole discussion is clouded by the question as to whether any adult in the temperate zone is free of this lesion.

*International Clinics.* A Quarterly of Illustrative Clinical Lectures and Especially Prepared Original Articles on Treatment, Medicine, Surgery, Neurology, Pediatrics, Obstetrics, Gynecology, Orthopedics, Pathology, Dermatology, Ophthalmology, Otology, Rhinology, Laryngology, and Hygiene. By Leading Members of the Medical Profession Throughout the World. Edited by HENRY W. CATTELL, A.M., M.D., Philadelphia. J. B. Lippincott Company, 1927. Vol IV, Thirty-seventh Series. Price in cloth, \$3.75.

This volume contains thirty-five articles, twenty-five of these being "Travel Clinics" representing well-known clinicians of London, Edinburgh, Frankfurt, Hamburg, Copenhagen, Stockholm and Oslo. There are three articles on Diagnosis and Treatment; two on Medicine; two on Surgery; one on Medical History and two on Post-graduate Study. There are 87 figures, two colored plates and numerous charts. The travel clinics consist of brief, interesting presentations of important subjects, and contain many valuable points and suggestions. Of

the American papers that by Hegner on the Clinical Diagnosis of Human Intestinal Protozoa is most timely in its scientific conservatism and should act as a control of the over-zealous and ignorant exploitation of human intestinal protozoan diseases that has been going on during the last several years. Harlow Brooks has also an exceedingly valuable practical article on The Treatment of the Patient with Pneumonia. Pugh's article on Stricture of the Urethra is also a valuable survey of the subject. Oliver's article on medical history, The Middle Ages, is interesting and entertaining.

*Contributions to Medical Science; Dedicated to Aldred Scott Warthin.* WILLARD J. STONE, B.S., M.D., F.A.C.P., Editor; and CARL V. WELLER, M.S., M.D., F.A.C.P., Professor of Pathology and Assistant Director of the Pathological Laboratories, University of Michigan, Chairman of the Editorial Committee. xxxii + 720 pages. Frontispiece and four special illustrations, 268 illustrations in text. Geo. Wahr, Ann Arbor, 1927. Price in fabricoid, carriage prepaid, \$10.00.

The appearance of an American medical *Festschrift* must meet with the approval of all who believe that there is a soul in medical education; and that it is fitting for mature students of Medicine, many years removed from the day of their graduation, to honor one to whom they owe much of the shaping of their scientific destiny. Such tributes have become altogether too few in recent years so that the advent of the present volume assumes additional significance. A group of his earlier colleagues, and pupils of both earlier and later years have dedicated this collection of their original medical investigations to Aldred Scott Warthin, A.M., Ph.D., M.D., F.A.C.P., Professor of Pathology and Director of the Pathological Laboratories of the University of Michigan, and also the Editor of the *Annals*, in honor of his sixtieth birthday, October 21, 1926, and of the completion of his thirty-fifth successive year of teaching in the University. The editors have found it possible to have one or more representatives for each of the thirty-five classes which Dr. Warthin

has taught. This unbroken sequence makes this volume almost unique among similar tributes. A Proem by Victor C. Vaughan and a Foreword by George Dock, both appreciative of Dr. Warthin's work in the University of Michigan, open the book. These are followed by fifty-four scientific contributions which are not arranged chronologically, as the purpose of the book might predicate, but are grouped according to their subject matter. Exception to this principal is found in the articles by G. Carl Huber, F. G. Novy and Peyton Rous, the first two early colleagues and the last at one time an instructor in Dr. Warthin's department. Huber describes a new method of fixing and staining central nervous system tissues for the purpose of studying cytoarchitecture. His paper emphasizes a method of approach which may be entirely new to many, the study of spinal cord tracts by means of microscopical sections in longitudinally oriented planes, running through several successive segments. Malcolm H. Soule collaborates with Novy in reporting some observations on the gas exchange of the bovine tubercle bacillus. The average respiratory quotient for this organism as grown on glycerol-agar was found to be 0.883; on glucose agar, 1.036; on serum agar, 0.852, and on plain agar, 0.888. Under the, to a pathologist, at least, intriguing caption of "Pathology and the Glare of the Future" to Peyton Rous includes both a plea and a prophecy—pathologists equipped with expert knowledge of fundamental science as well as first hand acquaintance with the processes of disease. A group of papers, dealing with Industrial Medicine follows. Alice Hamilton, in a most interesting survey, reviews the significant advances of the past fifteen years in the field of industrial toxicology. Carey P. McCord finds that the basophilic material in the red blood cells of laboratory animals to which benzol had been administered importantly exceeds the normal amount. Lyle B. Kingery describes the interesting occupational dermatomycosis, known among the packers of the Northwest as "fruit poisoning", as to etiology, symptomatology and pathology. Six articles on cardio-vascular physiology and pathology

provide a natural group. In the first of these Carl J. Wiggers reports a study of the genesis and mechanics of temporary ventricular alternation and in the second, *pulsus alternans* is considered from its clinical aspect by Roger S. Morris. A clinical study of 105 cases (from a total of 378) which showed upon electrocardiographic study a voltage not exceeding eight millimeters deflection in at least one of the leads I or II, is reported by C. T. Burnett with the collaboration of G. F. Pelz. The significance of such low voltages is discussed. George R. Herrmann demonstrates the electrocardiographic differentiation of primary from secondary dextrocardia, illustrating his thesis by three new cases of *situs viscerum inversus totalis* and contrasting the findings with those in three cases of the secondary type. Roentgenograms confirm the conclusions drawn from the electrocardiographic evidence. In view of Dr. Warthin's outstanding additions to our knowledge of cardiovascular syphilis it is not surprising to find that two contributors have chosen this subject. Interestingly enough, one of them, Harlow Brooks, presents the point of view of the internist in the treatment of this condition, while in the next essay an expert syphilographer, John H. Stokes, treats substantially the same subject matter, with additional observations on other forms of visceral syphilis. Cardiac pathology receives further consideration in the discussion of "Angina Pectoris and Coronary Occlusion" by Willard J. Stone. This article is based upon forty-six cases of coronary closure of which thirty-six came to autopsy. In a group of thirteen in which careful microscopical studies of the coronary vessels were made, syphilitic periarteritis was found in two instances. The histopathology of syphilis of the tonsil is described by Allen C. Starry. His photomicrographs are unusually good, especially those showing spirochetes. He finds that polymorphonuclear infiltration may characterize certain acute exacerbations of the syphilitic process. This brings tonsillar syphilis in accord, in this respect, with the similar infiltrations long known to exist in the syphilitic umbilical cord and with those

which Dr. Warthin himself first described for syphilis of the myocardium. Thyroid disease is presented through a series of clinical observations by James Rae Arneill, and the management of patients with toxic goiter is described by Richard R. Smith. E. B. Potter emphasizes the importance of the "Graves' constitution (Warthin)" by an analysis of twenty-two cases of exophthalmic goiter in which necropsy examination of the thymus was made. Hyperplasia of the thymus as well as general lymphoid hyperplasia was found. Another generalized disease of the lymphoid tissue is considered by Carl H. Fortune who finds that gross visceral infiltrations in generalized lymphoblastoma occur most frequently in the kidney and liver. The clinical response, and calcium and phosphorus metabolism, of infants with idiopathic tetany and rickets, under the influence of parathyroid extract administration, is made the subject of report by Lynne A. Hoag and a group of associates. This group of articles is continued by D. Murray Cowie and John P. Parsons, who find that hay fever and pollen asthma can best be treated by combining administration of pollen extracts with such environmental changes as the nature of the sensitization may indicate. Ralph R. Mellon discusses the newer biology of the bacteria, the untenability of the old morphologic concepts and the growing importance attaching to "cyclostages" in bacterial growth. That it is the hemolytic streptococcus alone which determines mortality in small-pox is the belief of J. G. Cumming. As a corollary it follows that the practitioner, by resorting to laboratory procedures, can make an early and reasonably definite prognosis in all cases of this disease. C. W. Edmunds found physostigmine of practically no value in the treatment of botulism in laboratory animals. Results with Congo red were only slightly more encouraging, but he believes that such experiments point the way to ultimate success by direct chemotherapy, combined with antitoxin, morphine and artificial respiration. Four articles dealing with tuberculosis are grouped together. Lydia M. DeWitt summarizes the results of her experiments with complex gold salts in the

chemotherapy of tuberculosis in guinea pigs. Difficult points in the differential diagnosis of renal tuberculosis, with illustrative cases, are discussed by Carl W. Eberbach, and Francis E. Seneor offers a very timely and helpful study of the general diagnostic importance of the tuberculides as frequently pointing to tuberculosis elsewhere in the body. From a consideration of the mechanism and physiology of artificial pneumothorax Warren C. Breidenbach concludes that this procedure should be applied to earlier cases than has been the custom in the past. Pneumothorax is recommended also by J. T. Watkins for certain suitable cases of lung abscesses, while for others bronchoscopy or pneumocautery drainage are the methods of choice. The value of Litten's phenomenon in determining the activity of the diaphragm and also that of the lung is the subject of Warren P. Elmer's contribution. Frank Smithies discusses parasitosis of the biliary tract and reports thirty-seven instances of protozoal infestation and one of *Necator americanus*. He believes that these conditions are of etiologic importance in a considerable variety of digestive disturbances. Variations in urobilogen output throughout the day and as affected by the taking of meals and by purgation are discussed by George B. Wallace and J. S. Diamond. These variations may affect the interpretation of this test as an index of liver function. H. S. McGee reports the results of an interesting study of bile secretion made upon a patient with biliary fistula. The ingestion of bile caused approximately a fifty per cent increase in the bile output. Three cases of oesophageal diverticulum form the basis of C. T. Sturgeon's paper. These were treated without a fatality by the two-stage operative procedure. Walter M. Simpson adds a new case and analyzes 150 human cases of aberrant pancreas found in the literature. Important clinical considerations are pointed out, such as the great frequency with which these aberrant glands are mistaken for neoplasms and their relationship to intestinal obstruction and intussusception. C. F. Tenney believes that gastric ulcers of types one, two and three of Cole's X-ray classification,

properly belong to the internist rather than to the surgeon. He utilizes the Smithies regime in the treatment of such ulcers. Five cases of diabetes, studied by W. M. Brace for periods of from thirty-two to forty-five months, failed to show under insulin administration any gain in total glucose tolerance. Insulin was found to have no more ability to arrest the downward progress of the disease than the earlier treatment without the drug. Each patient lost tolerance during the period of treatment with insulin. F. C. Hyde emphasizes the uncertainty of gross pathological diagnosis in the differentiation of new growths. Methods for the production of experimental oedema are described by Samuel R. Haythorn and the importance of such oedemas in studies on anthracosis, pigment phagocytes, the histogenesis of the tubercle and on the origin of the Langhans' giant cell is discussed. Warren to Vaughan describes the behavior of the omentum in the presence of particulate foreign matter, including dead germ substance, in experimental animals killed at intervals up to thirty-six days. A 1 to 800 aqueous solution of Janus green is recommended by Stuart Wilson as a selective stain for renal vessels and glomeruli. Air dried frozen sections are used following arterial injection. The lobular architecture of the spleen is described and figured by Ward J. MacNeal and by serial sections he demonstrates the existence of multiple or compound lobules. Splenic pathology is represented by Luther F. Warren's contribution describing a new case of Gaucher's disease. He also adds five new cases from the literature to the forty-nine tabulated by Cushing and Stout. Carl V. Weller discusses the phagocytosis of melanin in a case of generalized melanoblastoma. The reticulo-endothelial apparatus appears to exercise a selective phagocytosis for the precursors of melanin. The chemical composition of normal sweat and that from patients with senile eczema and with psoriasis has been studied by R. E. Barney. Differences in the amounts of nitrogenous substances and chlorides seem significant. No uric acid was found in twenty-nine specimens. A group of papers of surgical interest follows.



Carl E. Badgley describes, with X-rays of illustrative cases, the two-stage transplantation of fibula for tibia. Harold K. Faber writes most interestingly of craniosynostosis (oxycephaly and allied conditions) and recommends before the third year of life the excision of the synostosed sutures as the only means practicable for the conservation of vision. The history of total rhinoplasty is well told by Ferris N. Smith who also gives his own method for this procedure. Blood culture is considered by Harold T. Lillie to be the most important laboratory aid in the recognition of involvement of vessel walls and the blood stream in otitis media. Methods of handling such cases are discussed. R. B. Canfield and A. C. Furstenberg discuss the diagnosis of laryngeal carcinoma and give their method for laryngectomy under local anesthesia. That massive leakage of cerebro-spinal fluid may follow lumbar puncture is shown by a case detailed by Lester M. Wieder, in which there was good reason for believing that this was the deciding factor in the fatal outcome. The patient, however, had lues of the central nervous system, including the pituitary body. Theophile Raphael and Robert R. Dieterle describe a case showing the Korsakow syndrome, apparently in association with epidemic encephalitis, and

John L. Garvey gives the history with autopsy findings of a patient with adenocarcinoma mucosum of the parotid gland in whom generalized metastases caused the clinical picture to be dominated by an extradural spinal cord tumor syndrome. The two cases of adamantinoma of the pituitary region forming the basis of the paper by Max Peet offer an interesting study in contrasts, one being typical of the Fröhlich type while the other was of the Lorain group. Hugo A. Freund gives a clinical case in which high values for blood urea, non-protein nitrogen, creatinine and uric acid seemed to indicate a serious nephropathy. Only late in the disease was a brain tumor recognized and autopsy showed this to be the only significant pathological process present. An appendix to the volume gives a complete Aldred Scott Warthin bibliography up to October, 1926. While there can be no unity in a book of the nature of the one under review, beyond that of the purpose in the minds and hearts of its contributors, it is evident that each one has written in an untrammelled manner of the subject in which he was most interested. The average of the resulting contributions is distinctly higher than that found in current medical periodicals.

C.V.W.

## College News Notes

### DR. A. S. WARTHIN HONORED *By Publication of Volume of Contributions by Colleagues and Former Students*

In recognition of his thirty-five years as an outstanding teacher in the Medical School, and his international reputation as a pathologist, Dr. Aldred S. Warthin has been the recipient of an unique honor from his colleagues and former students, in the form of a volume entitled "Contributions to Medical Science." This book of 715 pages includes contributions from sixty-four authors, representing not only five of his early colleagues, Vaughan, Dock, Novy, Huber, and Rous, but also from one or more representatives from each of the thirty-five successive classes, who in the words of the editors, "has been proud to acknowledge Dr. Warthin as the greatest living teacher of pathology."

It was about eighteen months ago that a group of the medical alumni of the University got together and planned this volume in honor of Dr. Warthin's sixtieth birthday, October 21, 1927, and of the completion of his thirty-fifth year of teaching. The volume just published marks the completion of their labors. In one respect it is unique in *Festschriften* of this character because of unbroken sequence of papers coming from members from each of the thirty-five classes that have sat under Dr. Warthin.

On Tuesday afternoon, December 13, the formal presentation of the volume was made to the recipient. The opening address by Dean Hugh Cabot of the Medical School was as follows:

"It is characteristic of the Anglo-Saxon that he is generous in his commendations and appreciations of scientific men in other lands. He is likely to be very liberal in praise of his scientific brethren in his own country, particularly if they live at a dis-

tance and he rarely sees them, but he is emphatically not liberal in voicing his appreciation of his immediate colleagues and he rarely ventures to praise them if there is any danger that they may hear it. This perhaps springs from a fear of embarrassing them, from a fear of awakening in them emotions which they habitually suppress or from other laudable but mistaken motives.

"Be that as it may, the fact remains that we do rarely indulge ourselves in the luxury of telling our colleagues what we really think of the greatness of their work and the great effect they have produced in their field, both through their contributions and their teachings.

"It is, therefore, somewhat notable that we have come here this afternoon to behave in a most un-Anglo-Saxon fashion. We are about to give ourselves the pleasure of telling our colleague, Professor Warthin, how much we appreciate the amount, variety, and importance of his contributions to science and how well we recognize his skill as a teacher and the widespread and permanent effects which he has produced in advancing sound medical education. There is no one of his colleagues who can more skillfully throw off the cloak of our reticence and state more knowingly and appreciatively our true estimate of his value than his old friend and colleague, Professor Novy, and he will, therefore, make the presentation."

The formal presentation was then made by Dr. Frederick Novy, '87, a colleague of Dr. Warthin from the first.

"The Committee in charge has delegated to me the privilege and honor of acting in their behalf on this rare occasion. I appreciate this privilege the more so since it has been my good fortune to have known Dr. Warthin from the time he was a freshman on this campus.

"Dr. Warthin came to Michigan from Indiana University where he had been under the inspiring influence of two enthusiastic and great scientists, Dr. David Starr Jordan, who later became president of Leland Stanford University, and the late Professor Eigenman. It was at Michigan that he obtained an A.M. in 1890, and his Ph.D. in 1893. It was here likewise that he obtained his medical degree in 1891.

"His service in the University began in 1891 when the Chair in medicine had been newly filled by the appointment of Dr. George Dock, who with his unusual training in Internal Medicine and Pathology and because of his rare diagnostic ability was destined to become one of the great teachers of Medicine. Under him, Dr. Warthin served first as Assistant, then as Demonstrator of Internal Medicine. The stimulus that he then received is seen in the fact that while with him he spent three consecutive summers, 1893-1895, abroad in the study of medicine and pathology.

"In 1895 when the chair of pathology was vacated, Dr. Warthin was appointed Instructor in Pathology and served as such until 1899, when he became Assistant Professor. He was made Junior Professor in 1902 and finally, in 1903, Professor and Director of the Pathological Laboratory, which position he has held ever since.

"During all these years, notwithstanding the strain of teaching and of routine, Dr. Warthin followed his natural bent as an investigator and observer. It is impossible to mention here all of his publications. Suffice it to say that his studies on Hemolymph Glands, Blood-forming Organs, Anemias, Tuberculosis, Syphilis, Neoplasms, not overlooking his contributions to medical history, have won him his place in the front rank of American pathologists.

"Last year (1926) saw the completion of thirty-five years of service in this University. During that period over 3,000 students received the impress of his earnestness, and thoroughness, and of his devotion to science.

"It is a custom somewhat rare in this country, but less so abroad, for former pupils and associates to honor a great teach-

er and investigator by dedicating to him a Festschrift or Jubilee volume. It has been deemed appropriate to commemorate the thirty-five years of service and the 60th Anniversary of Dr. Warthin by a like observance.

"Dr. Warthin, on behalf of the committee in charge, I take the very great pleasure of congratulating you and presenting you with this volume which is dedicated to you. It contains contributions from your associates and from one or more pupils from each of the thirty-five classes which sat under your instruction. Accept it as an outward expression of the deep appreciation and respect of your old students and friends together with the hope that for many years to come you may carry on in full strength and vigor."

Dr. Warthin, accepting the volume, said:

"It is difficult to control one's emotion at such a time. No greater honor can come to a teacher than such tangible evidences as contained in this volume that his life-work has met with a fair measure of success, and that his teaching ideals have, in part at least, been justified. That so large a group of my old students could thus come together in such a notable demonstration of their creative interest and ability and of the possession of higher ideals of their profession than that of mere success in practice, makes me most happy and very proud of the thirty-five classes that have passed through my department. Still happier am I when I realize that this number is only a small proportion of my old students who are showing such ideals and ability for creative living, but out of necessity could not be added to the group represented in this volume. I can claim, however, only a small share in this result; it is collectively a product of the labors and ideals of my colleagues during these thirty-five years. The Medical School and the University as a whole may well be proud of its medical graduates. To my old students who planned and carried out this volume, to its editors, and to my old teachers and colleagues who have contributed to it, I give my most sincere thanks for this, the greatest honor of my life."

In addition to the fifty-seven articles included in this handsome volume an appendix, prepared by Dr. Carl V. Weller, presents a long list, filling some eighteen pages, of books and articles by Dr. Warthin, as well as his contributions to periodicals. Nothing could indicate so impressively the real accomplishment of Dr. Warthin in his chosen field. The volume itself is beautifully printed and profusely illustrated, with a portrait of Dr. Warthin as a frontispiece.

The list of medical alumni who contributed to the volume are by classes, as follows:

1892, Richard R. Smith; 1893, Alice Hamilton; 1894, James Rae Arneill; 1895, Harlow Brooks; 1896, David M. Cowie; 1897, George B. Wallace; 1898, Lydia M. DeWitt; 1899, R. Bishop Canfield; 1900, Fritz C. Hyde; 1901, Charles W. Edmunds and Willard J. Stone; 1902, Harry S. McGee and Roger S. Morris; 1903, James G. Cumming and Warren P. Elmer; 1904, Samuel R. Haythorn, Frank Smithies, Charles T. Sturgeon, and Charles F. Tenney; 1905, Hugo A. Freund and Ward J. MacNeal; 1906, John T. Watkins and Carl J. Wiggers; 1907, Charles Stuart Wilson; 1908, Clough T. Burnett; 1909, Ralph R. Mellon and Luther Warren; 1910, Max M. Peet and Ferris N. Smith; 1911, Harold K. Faber; 1912, Harold I. Lillie, Carey P. McCord, and John H. Stokes; 1913, Carl V. Weller; 1914, Francis E. Seneat; 1915, Albert C. Furstenberg; 1916, Carl W. Eberbach, Lyle B. Kingery, and Warren T. Vaughan; 1917, Warren C. Breidenbach; 1918, George R. Herrman and Lynne A. Hoag; 1919, Carl E. Badgley, Theophile Raphael, and John Purl Parsons; 1920, John L. Garvey; 1921, Robert E. Barney and Allen C. Starry; 1922, Lester M. Wieder; 1923, William M. Brace and Robert R. Dieterle; 1924, Walter M. Simpson; 1925, Eugene B. Potter; 1926, Carl H. Fortune.

The selection of the articles and the task of publication of the book was under the direct editorial supervision of Willard J. Stone, '01m, Pasadena, Calif., and Carl V. Weller, '13m, Professor of Pathology in the Medical School. The book was published by George Wahr, Ann Arbor.

#### A TRIBUTE AFTER THIRTY-FIVE YEARS' SERVICE

Few American teachers have been so honored by their colleagues and former students as has Dr. Aldred S. Warthin in the recently published "Contributions to Medical Science" issued as a tribute to his thirty-five years of service as a pathologist and teacher. Such volumes have been rare in America, though in the past they have not been uncommon in Germany, where it has been customary to honor outstanding teachers by the publication of *Festschriften* such as this. A similar volume was issued by the Medical School some years ago in honor of Victor C. Vaughan's long service to the University, and to medicine, while at Johns Hopkins, Dr. J. H. Welch and the late Sir William Osler were similarly honored.

It is safe to say, however, that very few *Festschriften* either in Europe or America have been so beautifully and elaborately produced, or so completely representative of the recipient's career as this one, containing as it does contributions from every class that has filled in their autopsy protocols under his watchful eye. Similarly it is significant that many of these contributors are among the most outstanding medical teachers in America.

The above report and editorial comment were taken from the Michigan Alumnus of January 7, 1928. The volume is reviewed from a scientific standpoint in this number. Both notices and review have been made at the request of a number of members of the College. Of the contributors to the volume the following are Fellows of the College:—Hugo Freund, Detroit; John T. Watkins, Detroit; C. S. Wilson, Detroit; Harlow Brooks, New York; Ward J. MacNeal, New York; C. F. Tenney, Jr., New York; Luther F. Warren, New York; Willard J. Stone, Pasadena; George Dock, Pasadena; S. R. Haythorn, Pittsburg; Frank Smithies, Chicago; Carl J. Wiggers, Cleveland; C. V. Weller, Ann Arbor; James R. Arneill, Denver; C. T. Burnett, Denver; F. E. Seneat, Chicago; W. C. Breidenbach, Dayton, Ohio; W. M. Simpson, Dayton, Ohio; and George R. Herrmann, New Orleans.

Dr. Osear B. Hunter (Fellow, February 24, 1926), Washington, D. C., Professor of Bacteriology and Pathology and Assistant Dean of the George Washington University Medical School, was recently elected the new head of the District Medical Society. Dr. Hunter is also the Pathologist to the George Washington University Hospital and Dispensary, consulting Pathologist to the Casualty, Montgomery County and Sibley Memorial Hospitals, as well as Professor of Bacteriology and Pathology at the Central training School for Nurses.

### OBITUARY

Dr. Albert Robin, Wilmington, Delaware (Fellow, March 10, 1923). Died December 23 of heart disease; aged 53.

Dr. Robin received his medical degree from the University of Pittsburgh School of Medicine in 1897 (then the University of Western Pennsylvania), and after pursuing postgraduate study at the Massachusetts General Hospital and at the Johns Hopkins University School of Medicine, moved to Wilmington and began his practice. He was known as the father of Wilmington's water filtration system and medical director of Hope Farm, the Delaware Anti-Tuberculosis Society's sanitarium. He was professor of pathology and bacteriology at Temple University School of Medicine from 1902 to 1907, director of pathology and bacteriology of the Delaware State Board of Health from 1899 to 1903, bacteriologist of the City Water Department in 1903, executive secretary of the Delaware State Tuberculosis Commission, and chairman of the medical board of the Physicians' and Surgeons' Hospital of Wilmington.

Dr. Robin was a member of the American Society of Bacteriologists, the American Public Health Association, the National Tuberculosis Association, the American Medical Association, the Delaware State Medical Association, the New Castle County Medical Association, assistant editor of the Atlantic Medical Journal and a member of the Board of Governors of The American College of Physicians.

### BOARD OF REGENTS MET AT MEMPHIS

The Board of Regents of The College met at Memphis, Tenn., November 12th and 13th, just preceding the annual meeting of the Southern Medical Association at the same place. Members of the Board who were present include Drs. Smithies (presiding), Brown, Jennings, Clement R. Jones, Lucas, Martin, Morgan, Murray, Piersol, Roberts, White, Marriott, Warthin and Mr. Loveland (Executive Secretary).

Their deliberations extended over two days during which a host of business matters were transacted, College policies discussed and other important matters attended to.

#### *Resignations Accepted*

Resignations were accepted from the following, subject to the return of the membership certificate in the case of Fellows:

#### *Fellows:*

Thomas Alsop, Donald Frick, W. H. Lewis, George M. Niles.

#### *Associates:*

Arthur R. Gibson, Ben H. Huggins, Grant H. Laing, Alfred S. Maschke, V. A. Neel, Henry C. Sears, Frank E. Wiedeman.

#### *Deaths Reported*

Deaths of those whose obituaries appear elsewhere in this Bulletin were reported.

#### *Fellowship Elections*

The following applicants were elected to Fellowship:

Anderson, Wm. Willis.....Atlanta, Ga.  
Baker, Gerdon E. ....Forty Fort, Pa.  
Bass, Elizabeth .....New Orleans, La.  
Bates, Lewis B. ....Aneon, Canal Zone  
Bernhard, Robert .....New Orleans, La.  
Bethea, Oscar W. ....New Orleans, La.  
Blair, A. A. ....Fort Smith, Ark.  
Boles, Russell S. ....Philadelphia, Pa.  
Brosius, Otto T. ....Almirante, Panama  
Campman, C. C. ....West Middlesex, Pa.  
Castlen, Charles R. ....Seattle, Wash.  
Clifford, Randall .....Boston, Mass.  
Comstock, Carl R...Saratoga Springs, N.Y.  
Crutehfield, E. D. ....Galveston, Texas  
Cunningham, Robert L..Los Angeles, Calif.  
Davison, Roland A...San Francisco, Calif.  
DeSautelle, W. T. ....Knoxville, Tenn.

Duval, Charles Warren..New Orleans, La.	Wilson George H. ....Lexington, Ky.
Elrod, J. O. ....Forsyth, Ga.	Wyatt, Bernard L. ....Tucson, Ariz.
Eustis, Allan ....New Orleans, La.	Wylder, Meldrum K..Albuquerque, N. Mex.
Finigan, John J. ....Rochester, N. Y.	
Fisher, Charles F. ....Brooklyn, N. Y.	<i>Resolutions Adopted</i>
Fleming, Wm. D. ....Washington, D. C.	Among the more important resolutions
Gregg, Harold W. ....Butte, Mont.	adopted were the following:
Hansen, Olga S. ....Minneapolis, Minn.	<i>Resolved</i> , That the Chairman of the
Hart, Wm. Lee ....Washington, D. C.	Board of Regents appoint a committee of
Heatley, John E. ....Oklahoma City, Okla.	three to devise ways and means to further
Huber, Edward Godfrey.....Atlanta, Ga.	the endowment fund of The College as
Hyman, Albert S. ....New York, N. Y.	specified by the Constitution.
Jacobs, Wm. F. ....Buffalo, N. Y.	<i>Resolved</i> , That the four following recom-
Janjigian, Robert R. ....Wilkes-Barre, Pa.	mendations of the Committee on Credentials
Kahn, I. S. ....San Antonio, Texas	shall be adopted in order to facilitate the
King, Hubert C. ....Lakewood, Ohio	work of that Committee:
Koch, Emil F. ....Brooklyn, N. Y.	1. Applicants who are not bona fide teach-
Lamb, Ellis ....Clinton, Okla.	ers or permanent laboratory workers shall
Lanford, John A. ....New Orleans, La.	be in the actual practice of medicine at a
Laubaugh, Ernest E. ....Boise, Idaho	permanent location at least five years before
Lepak, John A. ....St. Paul, Minn.	being considered eligible for Fellowship.
Levitt, Abel ....Buffalo, N. Y.	2. The Committee on Credentials, for As-
Lineback, Paul E....Emory University, Ga.	sociateship of the Board of Governors shall
Loeber, Maud ....New Orleans, La.	hold conferences with the Committee on
McCall, Daniel Thompson ....Mobile, Ala.	Credentials of the Board of Regents in
McGovern, Louis ....Brooklyn, N. Y.	order to correlate criteria and policies for
MaeDonald, John A ....Indianapolis, Ind.	admission to Associateship.
Matz, Philip B. ....Washington, D. C.	3. Applicants who fail to complete the
Mella, Hugo ....Washington, D. C.	requirements for admission to Fellowship
Milliken, Herbert E. ....Portland, Maine	within one year of date of filing applications
Morris, John M. ....Louisville, Ky.	shall be dropped, after suitable notification.
Myers, J. Arthur ....Minneapolis, Minn.	4. When an applicant has been in prac-
Peters, LeRoy S....Albuquerque, N. Mex.	tice fifteen years or less without making
Podlasky, H. B. ....Milwaukee, Wis.	any contribution to medical science, he
Pounders, Carroll M..Oklahoma City, Okla.	should be requested to submit fifty histories
Retan, H. Walden ....Syracuse, N. Y.	and five autopsies, or a suitable thesis.
Reynolds, Harold I. ....Athens, Ga.	<i>Resolved</i> , That The American College of
Roberts, Edwin H. ....Fort Sill, Okla.	Physicians hereby endorses the project of
Rogers, Thomas E. ....Macon, Ga.	the Gorgas Memorial Association.
Roller, Robert Douglas.Charleston, W. Va.	
Rueker, W. C. ....New Orleans, La.	
Saxl, Newton Thomas....New York, N. Y.	ANNALS OF INTERNAL MEDICINE
Schaefer, Robert L. ....Detroit, Mich.	In the report by the Editor, Dr. A. S.
Shillington, M. A. ....St. Paul, Minn.	Warthin, to the Board of Regents at Mem-
Silverman, Daniel N. ....New Orleans, La.	phis, announcement was made that the new
Snell, Albert Markley ....Rochester, Minn.	journal of The College, Annals of Internal
Steinwinder, C. D. ..San Antonio, Texas.	Medicine, is progressing satisfactorily and
Stone, Charles T. ....Galveston, Texas	that although it is still late in appearance,
Tihen, Henry N. ....Wichita, Kan.	several issues are almost ready for distribu-
Welch, Stewart H. ....Birmingham, Ala.	tion. It is anticipated that the past numbers
Whitmore, Eugene R. ..Washington, D. C.	will all be distributed during December or
Wightman, Orrin Sage..New York, N. Y.	the early part of January, and that there-
	after all issues will appear regularly.

## TWELFTH ANNUAL CLINICAL SESSION

### NEW ORLEANS COMMITTEES

JOHN H. MUSSER, *General Chairman*

#### *Committee on Arrangements*

JOHN H. MUSSER    ALLAN EUSTIS  
L. R. DEBUYS      ALDO CASTELLANI  
J. M. BAMBER      GEO. R. HERRMANN  
OSCAR DOWLING    HENRY DASPIT  
C. C. BASS          I. I. LEMANN

RANDOLPH LYONS

#### *Committee on Hall*

GEORGE R. HERRMANN

#### *Committee on Clinics*

I. I. LEMANN, *Chairman*

C. C. BASS            L. R. DEBUYS  
GEO. R. HERRMANN   RANDOLPH LYONS

#### *Committee on Hotels and Transportation*

J. M. BAMBER

#### *Committee on Entertainment*

HENRY DASPIT, *Chairman*

ALDO CASTELLANI    OSCAR DOWLING

#### *Committee on Publicity*

ALLAN EUSTIS, *Chairman*

C. C. BASS            OSCAR DOWLING

#### *Exhibits*

RANDOLPH LYONS

### GENERAL INFORMATION

*Headquarters:* Roosevelt Hotel.

Registration headquarters, railroad office, information bureau, the commercial exhibit and the general assembly hall are all located here.

Inasmuch as the Clinical Session will be held only twelve days after the annual Carnival, Mardi Gras, and since this city is a most popular winter resort for vacationists, reservations should be made longer in advance than has been customary in other Convention Cities.

*Who May Register—*

(a) All members in good standing for 1928 of The American College of Physicians. (As usual, bills for membership dues will be distributed on January 1, for 1928.)

(b) All newly elected members.

(c) All applicants for membership in The

College whose applications are still outstanding at the time of the Session.

(d) Members of the Orleans Parish Medical Society of New Orleans will be admitted to all general sessions as guests of The College and, in so far as space permits, will be assigned to special clinics, laboratory demonstrations, etc. (It is optional with them whether they secure Guest Cards at a fee of \$5.)

(e) Qualified physicians who may wish to attend this Session as visitors and who pay the nominal registration fee of \$5 and to whom "Guest Cards" are issued.

(f) Distinguished foreign visitors; physicians engaged in teaching or in scientific investigation; members of the Public Services of the United States, its possessions and Canada; retired practitioners of medicine and those who are pursuing studies in the various local colleges (in this group, all general meetings are open and, whenever possible, admission to special clinics and demonstrations will be arranged).

Blanks for all special clinics and demonstrations will be sent later with the program.

#### *Reduced Railroad Fares:*

Transportation to and from the New Orleans Clinical Session has been arranged on the Certificate Plan of fare and half fare. This applies to the railroads of the United States and the eastern part of Canada. Those who attend the Session will purchase going tickets at local railroad offices and at the same time request a "Certificate." This Certificate, when validated by the proper officer at the registration booth at New Orleans, will entitle members to purchase return tickets at half rate.

Reduced rates apply not only to members, but also to dependent members of their families.

Going tickets may be purchased from March 1st to 7th and the return tickets may be used up to March 13th. Those desiring to remain in New Orleans longer, in most instances, will be permitted to deposit their Certificates with the special railroad agent, Mr. W. H. Howard, located in the City Ticket Office of the Louisville and Nashville Railroad at New Orleans, upon

payment of fee of One Dollar (\$1.00), and be able to use return tickets, with departure from New Orleans up to and including March 24th.

### TENTATIVE PROGRAM

#### MONDAY, MARCH 5TH

##### OPENING SESSION—2:00 O'CLOCK

1. Addresses of Welcome, Honorable Arthur J. O'Keefe, Mayor of New Orleans; Albert Bledsoe Dinwiddie, Ph.D., LL.D., President, Tulane University of Louisiana; C. C. Bass, Dean of the School of Medicine, Tulane University of Louisiana.

2. Reply to Addresses of Welcome, Frank Smithies, President of The American College of Physicians.

3. Julius Bauer, Vienna, Austria.

4. David P. Barr, St. Louis, "Multiple Myeloma."

5. L. G. Rowntree and George E. Brown, Rochester, Minn., "Studies in Blood Volume with the Dye Method."

6. Joseph Sailer, Philadelphia. Title not yet announced.

7. Frank R. Menne, Portland, Ore., "The Effect of Iodin on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

##### EVENING SESSION, MONDAY—7:45 O'CLOCK

1. Maud Slye, Chicago, "Cancer and Heredity."

2. J. L. Goforth, Dallas, "Natural and Acquired Body Resistance to Neoplasia."

##### TUESDAY MORNING, MARCH 6—10 O'CLOCK

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."

2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."

3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."

4. Dr. C. C. Sturgis, Dr. Raphael Isaacs and Dr. Millard Smith: "Treatment of Pernicious Anemia with Liver Fraction."

#### Symposium on Tuberculosis.

5. Dr. Charles L. Minor. Title to be announced.

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

##### EVENING SESSION—7:45 O'CLOCK

1. Dr. James S. McLester. Title to be announced.

2. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

3. Dr. T. Z. Cason, "Some Unfinished Research Problems of the South."

##### WEDNESDAY MORNING, MARCH 7—10 O'CLOCK

1. Dr. L. F. Bishop, "The Practice of Cardiology."

2. Dr. Morris H. Kahn, "Heart Strain and its Consequences."

3. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

#### Symposium on Epilepsy

4. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

5. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

6. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

7. Dr. Tom Throckmorton. Title to be announced.

##### EVENING SESSION—7:45 O'CLOCK

#### Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."



4. Dr. J. C. Small, "Rheumatic Fever."
6. Dr. W. M. Simpson, "Tularemia."

#### THURSDAY MORNING, MARCH 8—10 O'CLOCK

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."
2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."
3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the View Point of an Internist."

#### Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."
5. Dr. Frederick M. Allen, "Present Results and Outlook of Jealietic Treatment."
6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."
7. Dr. W. H. Olmstead. "The Dietetic Management of the Diabetic in the Doctor's Office."

#### FRIDAY MORNING, MARCH 9—10 O'CLOCK

#### Symposium on Tropical Medicine.

1. Colonel Roger Brooke. Title to be announced.
2. Dr. Aldo Castellani. Title to be announced.
3. Dr. Wm. M. Jones, "The Early Lesions of Intestinal Amebiasis."
4. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.
5. Dr. Aristides Agramonte, Havana, Cuba. Title to be announced.

#### FRIDAY EVENING, MARCH 9—7:45 O'CLOCK

1. Dr. Julius Bauer, Vienna, Austria. Convocation Address.

The scientific program as given above will take about half of the time of the meeting. The remainder of the time will be occupied by clinics; In a general way these will be arranged as follows: In the afternoon from 1:45 to 4:30, clinics will be held at the Charity Hospital of New Orleans, Touro Infirmary, the Hutchinson Memorial,

the Richardson Memorial, Hotel Dieu, the Baptist Hospital, Mercy and Presbyterian Hospitals. At the Charity Hospital and Touro Infirmary, the program will be changed in the middle of the week, so that two separate programs will be put on at these two hospitals. The same will apply to the program at the Hutchinson Memorial. Clinics will be given at the Charity Hospital by Dr. George Bel, Dr. J. B. Guthrie, Dr. Amadee Granger, Dr. A. E. Fossier, Dr. J. L. Lewis, Dr. Randolph Lyons, Dr. J. H. Musser, Dr. Robert Bernhard, Dr. W. A. Love, Dr. George R. Herrmann, Dr. Philip Jones, and others. At the Charity Hospital, Dr. Julius Bauer, of Vienna, will give a clinic on certain days.

At the Touro Infirmary, clinics will be given by Dr. L. R. DeBuys and his staff and by Dr. I. I. Lemann and his staff. Dr. DeBuys' staff will limit themselves to diseases of children; Dr. Lemann and his staff to internal medicine and to subjects related to internal medicine more or less closely, so that it is quite possible with the present plan to have a surgeon to discuss cases in which the internist and the surgeon come into close contact, such as thyroid cases, abdominal conditions and so on.

At the Baptist Hospital, Dr. Oscar W. Bethea will run the program.

At Hotel Dieu, Dr. S. Chaille Jamison, Dr. Maurice Couret, Dr. L. A. Fortier and others will give clinics.

At the United States Marine Hospital, Dr. W. C. Rucker will be in charge of the program. There are always a large number of interesting tropical and unusual diseases at the Marine Hospital.

At the Hutchinson Memorial, clinics and demonstrations will be given daily. Dr. Wm. M. James and Dr. J. J. Vallarino, of Panama, will demonstrate their preparations and x-ray findings in amebiasis. Dr. J. C. Small, in addition to his scientific paper, will give in more detail than can be done at a large scientific meeting the particulars of the studies he has made in rheumatic fever. Dr. Robert S. Berghoff will give an afternoon demonstration on the diagnosis of chest diseases; Dr. T. J. Perkins, "Constitutional

Type in Relation to Mental Disease;" Dr. Aldo Castellani, "Fungus Growth;" Dr. C. C. Bass, "Malaria;" Dr. F. M. Johns; Dr. H. W. Butler, "A Slide Method for the Diagnosis of Syphilis;" Dr. Roy H. Turner, "Intestinal Microbiology." A clinical pathological conference will be given one or two days.

The program at the Richardson Memorial will be under the supervision of Dr. J. A. Lanford, who has invited Dr. C. W. Duval, Dr. Henry Laurens, Dr. Irving Hardesty and Dr. J. T. Halsey, Professors of Pathology, Physiology, Anatomy and Pharmacology, respectively, with their staffs, to demonstrate research problems that they are actively engaged in or which they recently completed.

Arrangements are completed for visits to the Leper Colony.

#### REDUCED FARES

Twelfth Annual Clinical Session, New Orleans, La.

The Executive Secretary advises that all railroads of the United States and of eastern Canada have granted reduced fares to our Clinical Session on the Certificate Plan of fare and half fare. Those who attend the Session will purchase going ticket at local railroad office and at the same time request a "Certificate." This Certificate, when validated by the proper officers at the registration booth at New Orleans, will entitle attendant to purchase return ticket a half rate.

These reduced rates apply not only to the attendant, but to dependent members of his family.

Going tickets may be purchased from March 1 to 7, and the return ticket may be used up to March 13. For those who desire to remain in New Orleans longer, the return ticket may be used until March 24, upon deposit of Certificate with W. H. Howard, Special Agent located in the City Ticket Office of the Louisville and Nashville Railroad, New Orleans, upon payment of fee of \$1.00 per Certificate receipt at time of deposit.

#### SPECIAL TRAINS

Twelfth Annual Clinical Session, New Orleans, La.

The Southern Railway System, in conjunction with other railroads of the East, have announced the "Eastern Physicians' Special" train starting from Boston, March 3d, passing through New York, Philadelphia, Baltimore, Washington, to arrive at New Orleans, Monday morning, March 5th. They also announce the "Central States Special," serving eastern Canada and eastern Central States, with connections at Cincinnati and joining the "Eastern Physicians' Special" at Chattanooga and continuing to New Orleans.

Of especial interest is the arrangement for a special train leaving New Orleans after the Convocation on Friday night, March 9th. Heretofore, it often became necessary for many who wished to attend the Convocation to remain over night, because of no suitable train accommodations being available after the Convocation Exercises. This special train has been arranged especially for the convenience of all members who attend the Convocation and wish to leave for the northeastern section of the country immediately thereafter. Time-tables are available in the Executive Secretary's office, and will be distributed to all members residing in the territories served by these special trains.

The route traversed includes the Piedmont Section of Virginia, Blue Ridge Mountain Range, the valleys of the Holston and the Tennessee Rivers, Historical Chattanooga, Industrial Birmingham and across Lake Pontchartrain.

Members residing in the territory served by these trains are requested to make use of them, inasmuch as their comfort and pleasure have been especially arranged for by having them travel together on these trains."

The Executive Offices have on hand a number of old YEAR BOOKS, 1923-24. While these have no present value from the standpoint of directory purposes (the new 1927-28 Year Book was issued during the summer), they may be of interest and his-

torical value to some of our members of more recent election. The Executive Secretary will gladly send a copy to any member upon receipt of 50c in stamps to cover cost of handling and mailing.

### NEW ORLEANS

*(Contributed by a Resident Fellow of the College)*

New Orleans, while more noted for its romantic charm and historic interest, is also a city of modern homes, churches, schools, libraries, beautiful parks and broad, well-paved highways. And it is a city blessed with a climate that makes for perennial out-door activity.

Summer in New Orleans doesn't die in September, shrouded in red autumn leaves. She just kisses the tips of her fingers to the Northland she's been visiting and skips back south again to the Gulf of Mexico where she was born. The Great Lakes can't follow her, nor rock-bound New England, nor the freezing Rockies, but the flowers trip behind her, and the birds go South, and the long steel heartstring of the railroads vibrate with the racing human trainful.

Volumes could be written about New Orleans and the many attractions the visitor will find within her gates. The architectural uniqueness of the building; its shady parks, wood-girded, and reminding one of the haunts of satyrs and nymphs; its inviting driveways, and its unusual historical associations, are features that appeal to all classes of visitors; it has magnificent hotels; its restaurants rank among the finest in the world; it has up-to-date and modern theatres; it has year-round balmy weather, and it has a gracious and hospitable citizenry who delight in entertaining you and know how to do so.

Even as New Orleans challenges the world to excel the charm of its French Quarter, so also does it point with proper pride to the picturesqueness of its surroundings as a whole—from the medieval beauty of the "Vieux Carré" to the newer city with its trees and flowers, beautiful homes, monuments, parks, streets, schools and churches.

The bulk of the architectural charm of

New Orleans—as well as of its historical and romantic appeal—is found in the "Vieux Carré," or old French Quarter, but by no means all of it. The larger city—the American City, that lies above Canal Street, has its gems of architecture, wonderful and costly mansions facing broad, tree-lined boulevards, beautiful parks and enticing driveways; churches, schools and libraries, magnificent federal, state and civic structures, and those wondrous works of the modern American builder, the skyscrapers that house the great commercial enterprises of today.

The homes of a city are probably the best indication of its prosperity and progressiveness as well as of the culture of its citizenry. Let us then tour over some of the main residential streets of New Orleans.

As we motor out St. Charles Avenue, note the delightful surroundings as well as the architectural beauty of the magnificent homes that border this world famous thoroughfare. There are mansions in St. Charles Avenue that well might rank as palaces, and opening into the street are a number of residence parks, also bordered and centered with palmetto palms—their latticed trunks too big to put your arms around; planted full of spicy camphor trees and long-fronded bananas, spaced out with graceful green fountains of Brazilian date palm.

The houses of the St. Charles district sit back in their gardens, honey-suckled, ivied, covered with jasmine vines, bouqueted by a dozen kinds of roses, with hibiscus torches flaming orange and red before them.

Esplanade Avenue also has its stately homes. It is the avenue of the aristocratic French families and extends from the river to Bayou St. John.

When the Sieur de Bienville, founder of New Orleans, came through Lake Borgne up through the Rigolets and then into the Bayou St. John, in 1718, Esplanade Avenue was an Indian path through a swampy wilderness. How long this trail had been used by the aborigines is not known, but Esplanade Avenue can well be said to be one of the oldest thoroughfares on the continent.

Esplanade Avenue was one of the boun-

daries of the old city as laid out by the Sieur de la Tour, who was Bienville's chief engineer, and became the aristocratic residence street of the latter Creole days. Many of these fine Creole homes, with their spacious grounds, remain.

Below Esplanade Avenue, in what is known as the Third District, is the residential section of small houses. Most of the streets are well paved, affording smooth roads for motoring.

Much of the architectural charm of New Orleans is also found in its old plantation houses. As the cypress swamps on the outskirts of the old city were cleared and turned into plantations, the plantation owners erected beautiful and expensive homes. The usual type is a large, square building surrounded on all four sides with an upstairs and downstairs gallery supported by enormous white columns.

These large plantation houses were built with slave labor out of material that could not be duplicated today at any price. There are also many beautiful ones that are small and compact, with small central portions with small wings balanced on each side. Sometimes there is a gallery on the central portion but not on the wings; and sometimes the galleries are on the wings and not on the central portion.

It has been truly said that "Churches prove the soul of a community"—that they illustrate the sincerity of purpose upon which consciousness is founded; that the city which looks well to its churches need never fear decadence or failure.

New Orleans has many wonderful ancient church structures still used for devotional purposes. New Orleans also has many handsome modern churches representing every denomination.

Christ Church Cathedral, Protestant Episcopal, stands in one of the prettiest portions of St. Charles Avenue at the intersection of Sixth Street.

The First Baptist Church, constructed of stone, is further up the avenue and presents an imposing appearance. A few blocks above is the Rayne Memorial Methodist Church and lower down the Avenue is the

costly and stately looking First Methodist Church.

One of the most attractive buildings on St. Charles Avenue is the Touro Synagogue, with its circular bronze roof. Temple Sinai, constructed on the plan of ancient Jewish houses of worship, is in Carondelet Street, further downtown.

Prytania Street Presbyterian Church is a massive structure of stone, in Prytania Street, a block from St. Charles Avenue. Napoleon Avenue Presbyterian Church is another splendid edifice of brick and stone construction. The First Presbyterian Church, which faces Lafayette Square, is one of the oldest of the Protestant churches in the city.

A recent addition to architectural New Orleans is the Mater Dolorosa Catholic Church in Carrollton Avenue. The Catholics have many other fine churches in the city, some of which are: Loyola Church, known as the "Little Jesuit Church," which is on the grounds of Loyola University, facing St. Charles Avenue, opposite Audubon Park; Church of the Immaculate Conception (Jesuits) in Baronne Street; St. Louis Cathedral, one of the most ancient church edifices in America, opposite Jackson Square; Church of the Holy Name, on St. Charles Avenue, and St. Joseph's Church, on Tulane Avenue.

The Christian Scientists have a very beautiful edifice, known as the First Church of Christ Scientist, located on the corner of Nashville Avenue and Garfield Street.

In other articles we have described New Orleans' wonderful museums, the Aquarium, the Art Gallery and other centers of culture. Just a word about its Public Library. The main library building, which was donated by Andrew Carnegie, is located at Lee Circle and St. Charles Avenue. It is of stone and marble construction and the architects copied the design of the Temple of Mars at Rome. The New Orleans library system, which includes the main library and twelve branches, ranks with the finest in the country.

New Orleans is a healthful city. The marked improvement in its health conditions in the past few decades is due in a large

*Commercial Exhibit*

When the Clinical Session takes place, make it a point, for the good will of The College and your own interest, to visit the exhibits. It will help us to retain the patronage of these companies both for exhibits and for advertising in *Annals of Internal Medicine*.

## Caribbean Cruise

When you are going on a trip, by land or sea, the first thought which flashes across your mind is "Shall I be comfortable?" For within the last decade travel is recognized as a pleasure and not merely as a method of getting from one place to another.

You demand change of scene, hope for

more Northern latitudes in July and August; rather the calm delightful atmosphere of a June afternoon. A land where Westerly Trade winds bring health and healing in their train, where the sapphire sea ripples over coral reefs in lazy content and where, after gorgeous sunsets, the stars gleam like golden lamps in an indigo sky.

Ponce de Leon sought for a Spring of Perpetual Youth unaware that all around him was the rejuvenating sea and air and sky which in the passing years have brought renewed health and spirits to the thousands who have experienced the charm of the Caribbean.

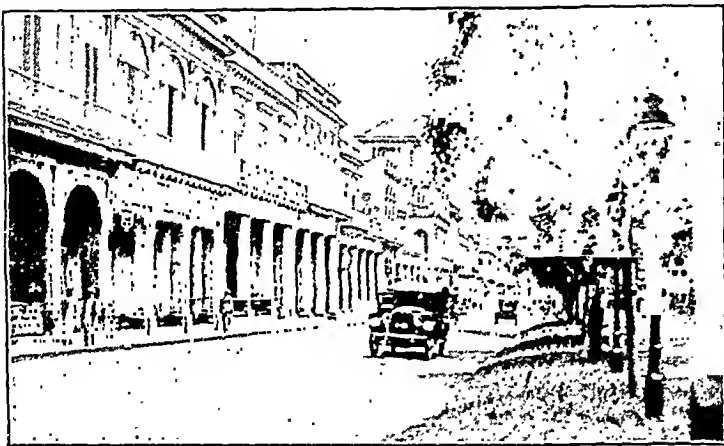
pleasant weather, and insist upon good food, facilities for bathing and dressing, and in addition to these requisites, away down deep in your heart is the thrill of adventure that comes from the desire to see new countries and new people.

What can offer you more than the Caribbean:?

With this in mind a post convention cruise to Havana, Cuba, Panama Canal Zone, and other Caribbean countries is being offered for our members and their families by the United Fruit Company on one of the steamers of its Great White Fleet, the S. S. Cartago.

The steamer will sail from New Orleans on March 10th, returning March 26th and during that time will visit lands of perpetual summer. Not the scorching heat of our

leaves more than a passing impression. It has the undefineable charm of good music, wonderful architecture, of beautiful women; and every year visitors from all parts of the world return knowing that they will find something new, something delightful to



rangements as early as possible. Reservation requests should be accompanied by a deposit of fifty dollars (\$50.00) per person, balance to be paid not later than February 25th. Reservations should be secured directly through one of the following officials of the United Fruit Company:

H. C. Hicks, A. P. T. H., United Fruit

Company, 321 St. Charles Ct., New Orleans, La. L. P. Jones, G. W. P. A., United Fruit Company, 203 S. Dearborn St., Chicago, Ill.

Further information and literature will gladly be supplied upon request to the officers mentioned, or inquiries may be sent through the Executive Secretary's office in Philadelphia.

# Regeneration of Tubular Epithelium in the Human Kidney Following Injury by Mercuric Chloride

BY WARREN C. HUNTER, M.A., M.D.\*

IT IS rather generally believed that the functional epithelium of the human kidney has only a limited regenerative capacity and that the clinical importance of this is negligible. The matter receives little or no consideration in most systems and textbooks of medicine and pathology. Yet in the voluminous literature on renal diseases are many descriptions of regeneration in the kidney of man and experimental animals, particularly after injury by the salts of heavy metals.

As long ago as 1879 Weigert (1) noted regeneration in the renal parenchyma of animals poisoned with chromic acid. Likewise Thorel (2) (1903) found marked evidence of regeneration in the kidneys of experimental animals within eight days after the administration of chromic acid. Heineke (3) (1909) in a study of a series of human cases in which death occurred from a few hours to several weeks after taking sublimate, noted that extensive cellular regeneration had taken place in the affected tubules. A remarkable

experimental study of tubular cell regeneration is that of Oliver (4) (1915) who showed that in animals given a single injection of uranium nitrate there is regenerative activity in the epithelium of the damaged tubules as early as the fourth or fifth day after the injury and that the process continues until the tubules are completely relined by new cells. In a recent study of the pathology of the sublimate kidney in man Nakata (5) (1922) has also described the formation of new cells in the affected tubules. The list might be greatly lengthened but the references cited are sufficient to show that the recognition of cellular regeneration in the kidney is neither new nor rare.

In view of the importance of the possibility of the growth of new epithelium to replace that lost in the course of renal disease in man, and because of the apparent lack of its recognition in the medical textbooks, the writer felt it might be of interest to record the observations made in a recent case illustrating the point.

The following clinical data were furnished by Dr. Earl Smith, clinician in charge:

\*From the Department of Pathology, University of Oregon Medical School, Portland.



## CASE HISTORY

R. MacD., female, age 41. Single. Occupation—laboratory technician.

## PAST HISTORY

Well until ten years ago at which time she suffered a nervous breakdown. Since then has been nervous and at times despondent.

On August 20th 1926 she took by mouth two  $7\frac{1}{2}$  grain tablets of mercuric chloride. The stomach was promptly emptied, egg albumin was given and the patient subjected to repeated sweating. No apparent ill effects developed and she was discharged after thirteen days apparently fully recovered.

## PRESENT ILLNESS

July 10th 1927, following a period of mental depression she again took bichloride. The exact amount was unknown but the patient stated that she had swallowed a "handful" of tablets. (1.82 grains each). She was not found until about two hours after taking the poison. The stomach was then immediately pumped, following which egg white, magnesium sulphate and sodium bicarbonate were administered. There was considerable pain in the epigastrium, incessant vomiting of blood tinged fluid and profuse bowel movements. Within a few days there developed a marked mercurial stomatitis.

Following is a record of the daily urine output:

1st day.....	anuria
2d " .....	"
3d " .....	"
4th " .....	5 ccs. per catheter
5th " .....	10 " " "
6th " .....	30 " " "
7th " .....	90 " " "
8th " .....	60 " voided
9th " .....	105 " "
10th " .....	270 " "
11th " .....	270 " "
12th " .....	135 " "
13th " .....	750 " "

The urine was at all times alkaline in reaction and showed a four plus albumin content. At first no casts were present but later granular, epithelial and hyaline types appeared as well as leukocytes and erythrocytes in considerable numbers.

On the twelfth day there developed a severe diarrhea with frequent bloody stools having a foul odor. This persisted and increased in severity the last two days of life. There was also considerable hemorrhage from the lesions in the mouth. Toward the end the patient had frequent convulsions which could be controlled only by morphine and repeated inhalations of chloroform. Death occurred on the fourteenth day after taking the poison.

AUTOPSY (*Abridged*)

U. of O., Pathology No. 17,293.

The body is that of a small-statured fairly well nourished female 41 years of age. There is no evidence of injury or disease about the head or neck. The gums have been sutured by the embalmer and the oral cavity is accordingly not examined. The body is embalmed; body heat is absent; rigor mortis is present.

The colon and the greater part of the small bowel are distended and contain a dark bloody fluid. The mucosa in many places is diffusely reddish from hemorrhage but no foci of diphtheritic inflammation are found.

The kidneys are increased in size, each weighing 195 grams. The capsule strips readily exposing a smooth pale cortical surface. The surfaces made by sectioning reveal the cortex to be pale and swollen. The normal markings here are somewhat indistinct. There are no noteworthy gross changes in the medulla or pelvis.

The lungs are dark and boggy. On section there appears to be a moderate degree of passive hyperemia. About a number of the smaller bronchi are small patchy consolidations.

All other noteworthy pathological changes are listed in the pathologic diagnosis. Organs and tissues not mentioned are normal.

## MICROSCOPIC

*Kidneys:* Most striking is the great reduction in the number of proximal convoluted tubules retaining the original epithelial lining. Instead most of these tubules are lined by cells differing widely from normal in both morphologic and staining characteristics. The cells are often flattened and elongated with nuclei poor in chromatin and exhibiting not infrequently beautiful premitotic and mitotic figures. In other tubules the cells may be quite irregularly shaped, at times columnar or even triangular. Occasionally tubules are found in which the young epithelial cells are projecting far into the lumen and there surrounding fragments or even necrotic cells, the cytoplasmic processes of the new cells pushing between the bits of debris and forming a network about the masses. Nearly everywhere the damaged tubules are almost fully relined by the types of cells above described. In addition to the abnormal morphology the regenerated epithelium is further distinguished from the original proximal convoluted tubular cells by the staining reaction of the cytoplasm. In hemotoxylin and eosin preparations this has a distinct bluish-pink appearance in contrast to the normal pinkish-red. This characteristic together with the abnormal shape makes it very easy to recognize the new cells.

No changes are detected in the epithelium of any of the tubules other than the proximal convoluted group. The glomeruli exhibit no noteworthy histological alteration. The interstitial tissue is everywhere edematous and in the medulla one sees fairly numerous collections of small lymphocytes. Beginning proliferation of the intertubular connective tissue is evidenced by the presence of mitoses in a few cells. Casts are not abundant in the tubules within the cortex but are fairly numerous in the larger collecting tubules in the medulla. The casts are mostly of the hyaline variety but some are made up of granular cellular debris with some admixture of erythrocytes. Calcification is not in evidence. (See Figs. 1, 2, 3, 4.)

*Colon and Ileum:*—Post-mortem necrosis of superficial epithelium; diffuse hemorrhage in the submucosa.

All noteworthy findings in the other organs are listed in the pathologic diagnosis.

## PATHOLOGIC DIAGNOSIS

Acute mercuric chloride nephritis with extensive regeneration of epithelium in the affected tubules;

Acute mercuric enterocolitis with hemorrhage;

Intra-alveolar pulmonary hemorrhage, passive hyperemia, edema, purulent bronchitis and early bronchopneumonia;

Chronic salpingitis, probably tuberculous; Atrophy of uterus and ovaries;

Brown atrophy of myocardium and liver; Parenchymatous degeneration of liver.

## COMMENT

Microscopically the kidney shows evidence of a widespread injury to the proximal convoluted tubules which has been followed by cellular regeneration so extensive that the tubules are almost completely relined by a new and atypical cell differing very markedly from the original epithelium in size, shape and staining qualities. The degree of repair which has taken place within the short space of fourteen days is truly remarkable.

The case offers an excellent opportunity of comparing the process of regeneration with that which I have observed in the rabbit kidney. In an experimental study (6) it was found that regeneration of tubular epithelium begins almost constantly on the fourth to fifth day following the administration of sublimate. The new cells are derived largely by mitotic division of injured but still viable cells in those segments of the proximal convoluted tubules on which mercuric chloride acts

selectively and to a lesser extent from epithelium proximal and distal to the injured area. In the rabbit proliferation of cells, once it has begun, goes on very rapidly so that after twelve to fourteen days the tubules are fully

phagocytic phenomenon. It appears to me to be rather the result of retention of the loosely packed necrotic epithelium in the tubules until after the new cells have begun to grow. The appearance of phagocytosis of the debris is

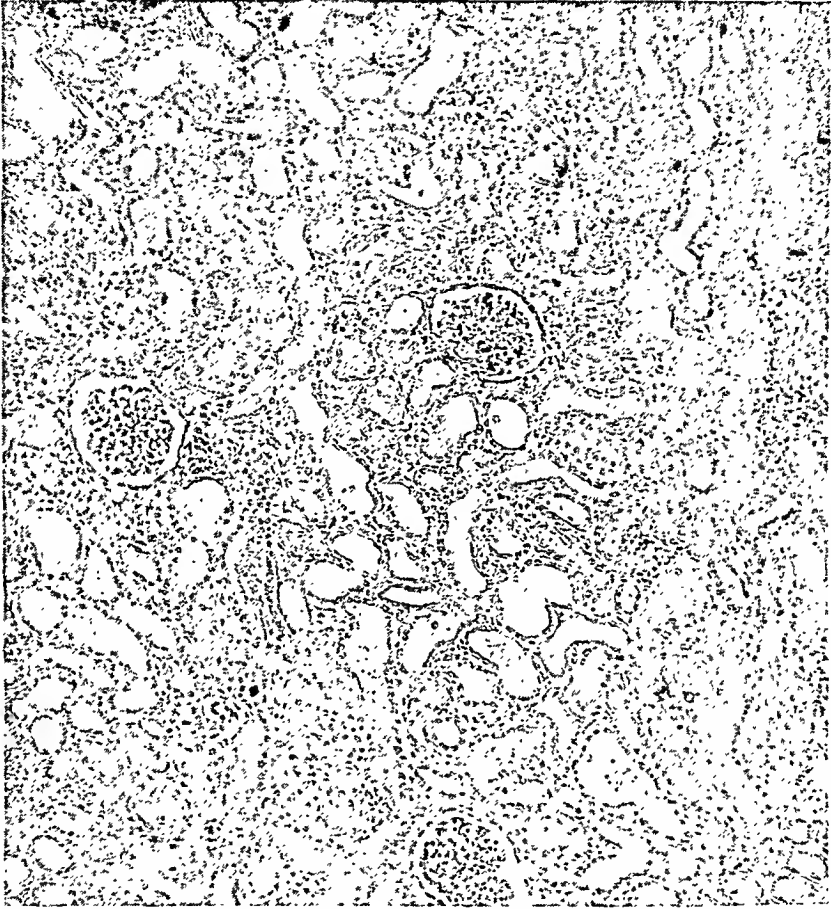


FIGURE 1.—Low power microphotograph of kidney cortex showing part of a labyrinth and medullary ray. Many segments of the proximal convoluted tubules are lined by regenerated epithelium. The small size and atypical flattened shape of these cells is the cause of the apparent dilatation of the affected tubules.

lined by cells having exactly the appearance of those described in the human kidney under consideration. The new cells in the rabbit likewise show a tendency to push between necrotic masses in the lumina of the tubules. Heineke (*loc. cit.*) saw this in the human kidney and believed it to be a

merely the result of the growth of the cell cytoplasm along the line of least resistance which often takes it into the spaces between the dead matter.

The regenerated cells have the staining reaction of embryonic epithelium. In the rabbit this persists over a period of several months and is very probably

permanent. To a lesser degree the abnormality in cell outline is found for a long time after completion of the reparative process. These features, together with the sharp localization of the injury to the proximal convoluted tubules, make it difficult to confuse the

the seventh day 90 cubic centimeters were obtained. From this time the urine excretion increased daily, reaching a total of 750 cubic centimeters on the day before death. The quantity of urine is of course in large measure dependent upon the condition of the

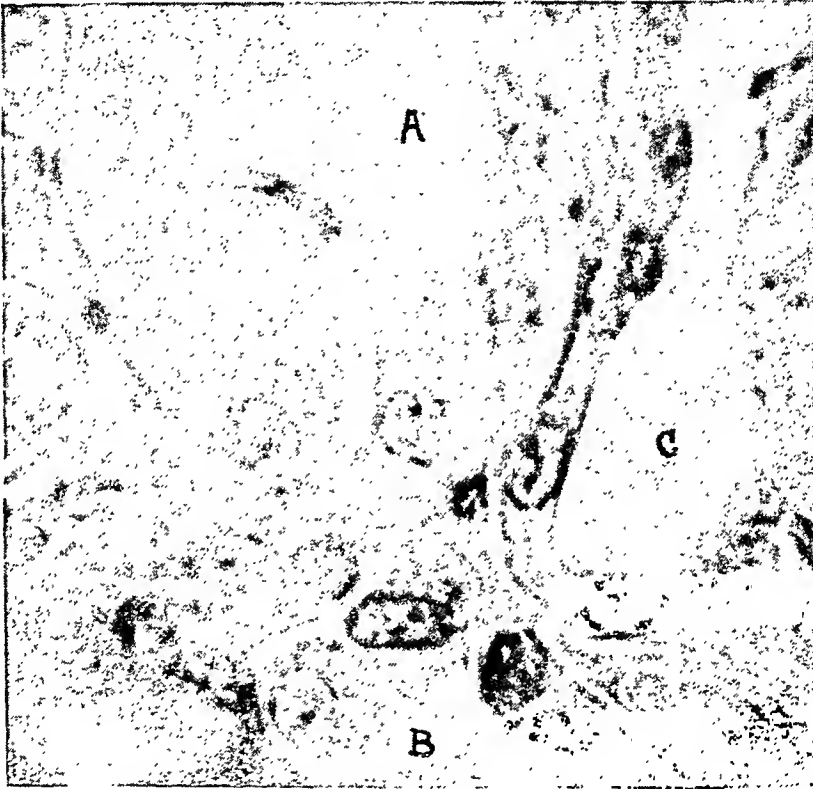


FIGURE 2.—High power microphotograph. (a) is a portion of proximal convoluted tubule in which the original epithelium has not been destroyed. At (b) and (c) the same tubule exhibits the type of cell characteristic of regenerated epithelium in this location. Note the striking contrast in the appearance of the two types of cells.

new epithelium with that of the descending limb of Henle to which it bears some resemblance.

Clinically the question as to functional ability of regenerated epithelium is of paramount interest. In the case at hand it would appear that the new cells were functioning. The combined urine output during the first six days was only 45 cubic centimeters. On

glomeruli and although in microscopic sections these may exhibit no changes there may nevertheless have been severe functional injury with gradual recovery beginning at about the same time as the tubular repair. In any event it is seen that the kidneys were almost completely healed at the time of death and the urine output indicates increasing functional activity. It is quite



FIGURE 3.—Regeneration of renal tubular epithelium. The arrow points to a cell in mitotic division. The lumen of the tubule contains granular cellular debris. Near the mitotic figure are several newly formed epithelial cells. High power.



FIGURE 4.—High power photomicrograph illustrating the manner in which young epithelial cells (a) and (b) grow over and enclose necrotic cellular material. The same process is shown at (d). (e) is a tubule lined by typical regenerated epithelium.

possible that had not the intestinal lesions of mercury supervened the patient might have recovered. Whether or not secondary contraction of the kidney would have developed later is problematical. In rabbits repeatedly poisoned with small doses of sublimate such a change is in my experience almost uniformly present. It is possible that in the human kidney under consideration we are witnessing in the early proliferation of the stroma the first step in the direction of secondary contraction. Because of the lack of any urinary findings following the first poisoning a year before death it is impossible to say whether or not any of the regenerated epithelium dates from that time but the clinical course would indicate that there was no appreciable kidney damage.

#### SUMMARY

1. An instance of mercuric chloride poisoning in the human is presented in which the kidney exhibits al-

most complete regeneration of the tubular epithelium within fourteen days after injury.

2. The microscopic appearance of the kidney is strikingly similar to that observed in experimental animals at the same interval of time after sublimate poisoning.

3. The regenerated epithelium differs markedly from the normal in its histological and staining characteristics, thus facilitating easy and certain recognition.

4. Microscopic proof of healing and clinical evidence of increasing function indicate that the kidney was recovering from the effects of the poison.

5. Death was due in large measure to the intestinal lesions of mercury and terminal bronchopneumonia rather than to renal insufficiency.

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# A Study of 22,808 Blood Sugar Estimations— Fasting and Postprandial—in Non- Diabetic Individuals

BY HENRY J. JOHN, M.D., F.A.C.P., *Cleveland Clinic, Cleveland, Ohio*

A YEAR ago I analyzed the fasting blood sugar estimations in one thousand non-diabetic patients taken at random as they had presented themselves at the Clinic for various examinations. Previous to that time I had had the impression that with each advancing decade of life the fasting blood sugar rose within reasonable limits, so that, for example, in the sixth decade as much as 150 mg. of sugar per 100 c.c. of blood might be considered as a normal figure. My study of this series of 1000 cases disillusioned me in this respect, though in each decade there was a slight average rise in the fasting blood sugar, as is shown by the fact that it varied from 91.8 to 107.4. The average figures for the various decades are given in Table I.

The actual range of the fasting blood sugar in this group was from 60 to 189 mg. per 100 c.c., the few high figures appearing in patients afflicted with diseases of the kidneys.

The study here presented comprises an analysis of 22,808 blood sugar estimations including fasting blood sugar estimations and estimations made in the course of glucose tolerance tests. In each of these groups of tests there

are, as one would expect, some variable factors which may have influenced the blood sugar content, such as the type and the caloric value of the last meal, the patient's mental condition, the effect of any disease which may have been present. None of these has been taken into consideration in this study, the purpose of which has been to present the findings in an unselected series of clinical cases as they have appeared for examination, with the exception that diabetic individuals have been excluded. To study the effect of each variable factor in each case would be almost an impossible task, and the result could not but be inaccurate, so that on the whole I feel that the present analysis will shed some light on existing conditions.

All the blood sugar analyses were made with oxalated blood, 10 mg. of potassium oxalate per 10 c.c. of blood; the actual estimations were made within a few minutes after the blood was taken and picrated, 1 c.c. of whole blood being used for the estimation, which was done by the Myer-Bailey method.

I was led to undertake the present analysis by the comparatively frequent finding of low blood sugar values—65

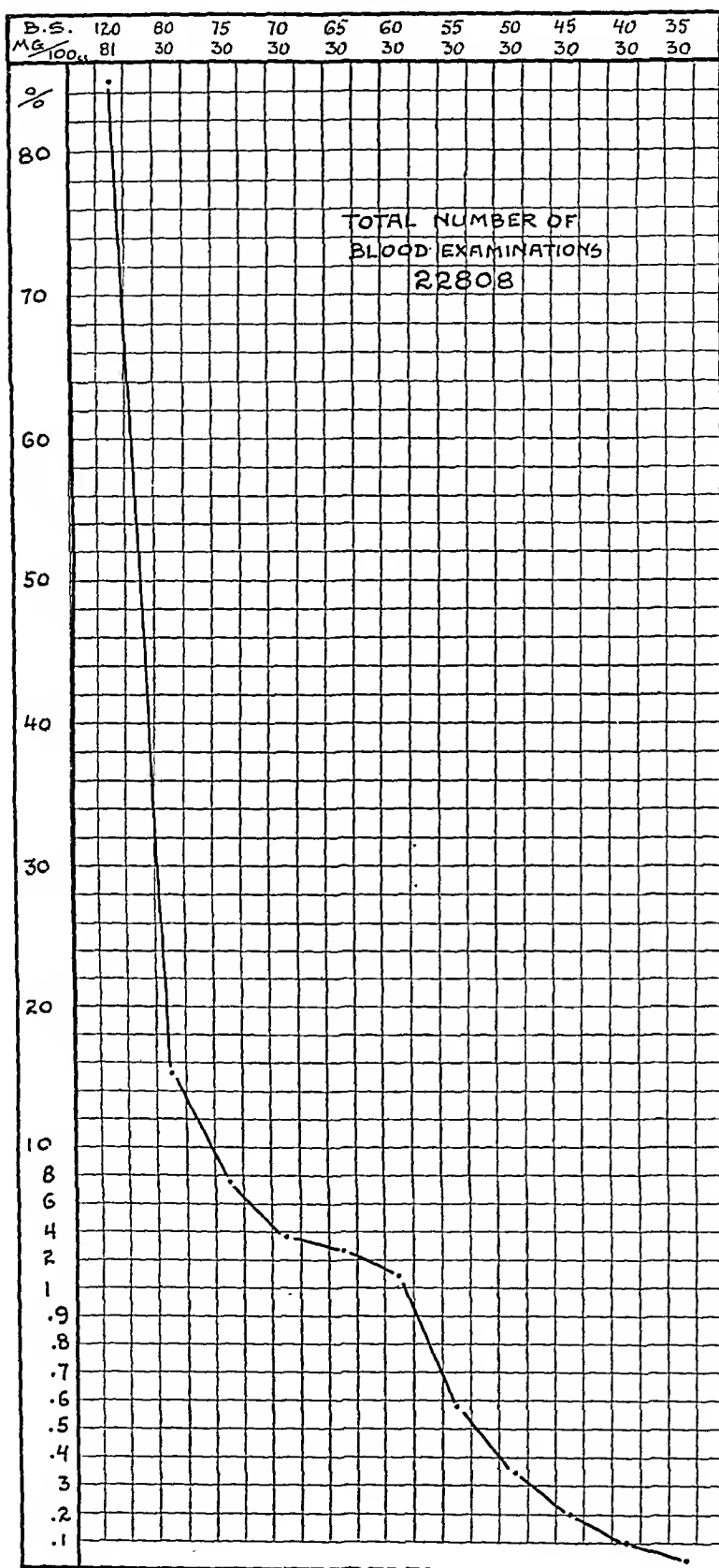




TABLE I

Average Fasting Blood Sugar Level in the Different Age Decades, As Shown by Blood Sugar Estimations in 1000 Non-Diabetic Individuals

Age Decade	I	II	III	IV	V	VI	VII	VIII
Aver. Bl. Sug. mg/100 c.c.	91.8	94.0	96.4	98.0	100.9	101.0	102.7	107.4

or fewer mg. per 100 c.c., in 494 cases of this series. I was anxious to see how often a low blood sugar content occurs in non-diabetic individuals; if possible, to see what might be the explanation of this low value; and to determine the relation of the low content to the ingestion of food. In an attempt to discover this last relationship the accompanying series of graphic charts (II-XV) was constructed.

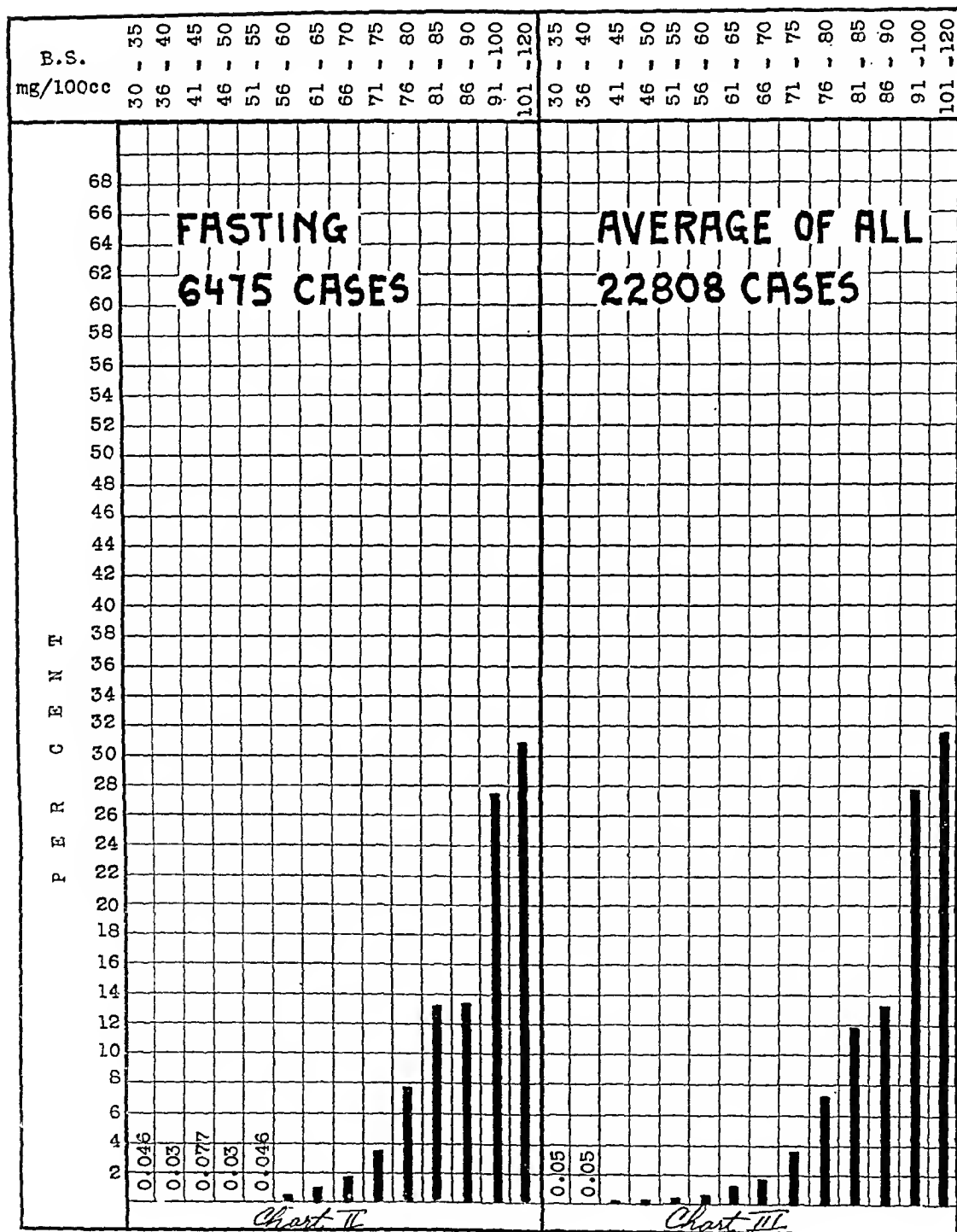
In Table II are given figures in accordance with which these graphs were made. The figures for more than six hours after the ingestion of glucose could perhaps be considered as representing fasting blood sugar values, in which case the total number of fasting blood sugar estimations would be 7644 in place of 6475.

Table III shows the percentile relation between the total number of estimations (22,808) and the number of estimations in which the blood sugar was found to be below certain levels. These figures show clearly that the generally accepted idea that the range of normal non-diabetic blood sugar is from 80 to 180 mg. per 100 c.c.—depending upon the postprandial period—is incorrect; for in this series in 2452 estimations, or 15.14 per cent, the blood sugar was below this level. (See Chart I and III). Moreover, in the series of fasting blood sugar estimations (6475), in 954, or 14.73 per cent, the blood sugar values are 80 mg. per 100 c.c. or less, running as

low as 30 mg. per 100 c.c. in these cases. (Chart II).

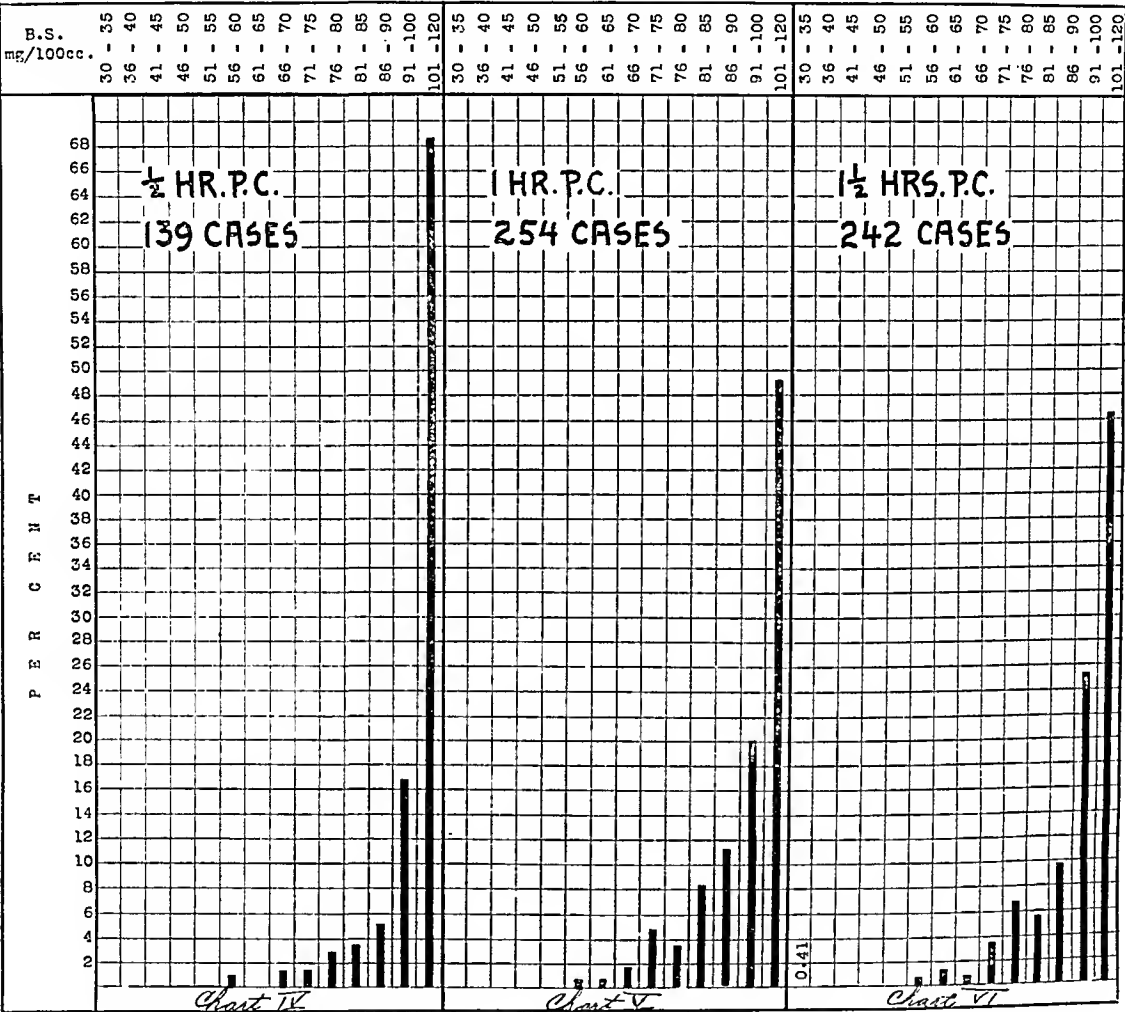
From glucose tolerance studies one finds that following the ingestion of 100 gm. glucose, in a non-diabetic individual there are two types of response—a moderate rise as high as 180 mg. per 100 c.c. in from one-half to one hour, with a return to the normal level at the end of one, one and one-half or two hours, or practically no rise whatever. In non-diabetic individuals one would expect to find a considerable rise at the end of the half hour and hour periods after the ingestion of glucose. However, I have not included in this report blood sugar values above 120 mg. per 100 c.c. for the reason that these higher values rarely appear on our records, as they have no diagnostic value whatever in the case of non-diabetic individuals. These estimations were made only when the blood was taken to determine the presence or absence of some other metabolite, the blood sugar estimation being then made for scientific purposes only. However, Charts IV and V offer the interesting observation that during the first hour after the ingestion of glucose, in only 0.5 per cent of the cases the blood sugar value was 56 mg. per 100 c.c. or below.

In individuals who are strictly normal (as far as their insulogenic function is concerned) the blood sugar value one and one-half hours after the ingestion of glucose should be at the



normal level. The postprandial blood sugar curves usually show a more or less marked hypoglycemic “dip” after the primary postprandial rise, this being manifested chiefly at the end of the two and one-half and three and one-half hour periods, but, as can be noted from Chart VI, it appears during the

hypoglycemia is produced. In such cases the insulogenic apparatus may be considered to be hypersensitive, and this result has been described in the literature as “hyperinsulinism”. This is the opinion of Depisch and Hase-nöhl.(2) Physical work brings about the same result, but, as I believe, in a



earlier period in a considerable number of cases. This “postprandial hypoglycemic dip” I think can be explained as being probably due to the primary stimulation of the insulogenic apparatus by the ingested food, with a consequent heavy outpouring of insulin which, so to speak, burns up more than the normal amount of sugar so that the

different manner. Physical work results in a consumption of the muscle glycogen, which requires insulin. The secretion of the insulin once started continues as long as there is a demand for it, and if the liver is poorly stocked with glycogen, or if the demand for glycogen continues for too long a time so that the supply can not cope with

TABLE II

*An Analysis of 22,808 Blood Sugar Estimations*

(The figures represent the number of estimations in which the blood sugar was at the level indicated by the values given at the top of the columns.)

B. S. mg.	30	35	40	45	50	55	60	65	70	75	80	85	90	100	105	110	115	120	Total
pr. 100 c.c.	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	
Time																			
Fasting	3	2	5	2	3	14	55	118	237	515	850	889	1784	1998	6475				
½ hr. p. c.							1		2	2	4	5	7	23	95	139			
1 hr. p. c.							1	1	5	12	9	21	29	51	125	254			
1½ hr. p. c.	1						1	3	1	9	16	14	24	61	112	242			
2 hrs. p. c.			1	3	6	6	17	15	31	54	97	95	203	381	910				
2½ hrs. p. c.					1	4	3	12	26	53	105	120	281	392	997				
3 hrs. p. c.	3	5	10	15	18	32	54	61	100	180	256	330	721	953	2738				
3½ hrs. p. c.				2	1	1	10	23	59	112	176	234	472	621	1711				
4 hrs. p. c.	4	4	7	9	18	33	58	80	143	220	357	391	859	860	3043				
4½ hrs. p. c.				1	3	3	15	19	60	117	199	228	511	477	1633				
5 hrs. p. c.				1	3	6	24	43	114	215	357	403	766	695	2627				
6 hrs. p. c.					1		11	21	26	77	137	145	256	196	870				
More than 6 hrs.					1	2	5	10	58	99	158	140	372	324	1169				
Total	11	12	23	33	55	104	256	410	877	1671	2732	3035	6360	7229	22808				

TABLE III

## The Percentage Relation of the Different Blood Sugar Findings

	Total	Per Cent
Total number of blood sugar estimations	22808	100
Blood sugar from 81 to 120 mg. per 100 c.c.	19356	84.86
Blood sugar 80 mg. per 100 c.c. or less	3452	15.14
Blood sugar 75 mg. per 100 c.c. or less	1781	7.81
Blood sugar 70 mg. per 100 c.c. or less	904	3.96
Blood sugar 65 mg. per 100 c.c. or less	494	2.16
Blood sugar 60 mg. per 100 c.c. or less	238	1.04
Blood sugar 55 mg. per 100 c.c. or less	134	0.58
Blood sugar 50 mg. per 100 c.c. or less	79	0.34
Blood sugar 45 mg. per 100 c.c. or less	46	0.20
Blood sugar 40 mg. per 100 c.c. or less	23	0.10
Blood sugar 35 mg. per 100 c.c. or less	11	0.04

the demand, hypoglycemia is apt to occur.

The end of the second postprandial hour shows a definite increase in the number of low blood sugar values and a relative decrease in the higher values. (See Chart VII).

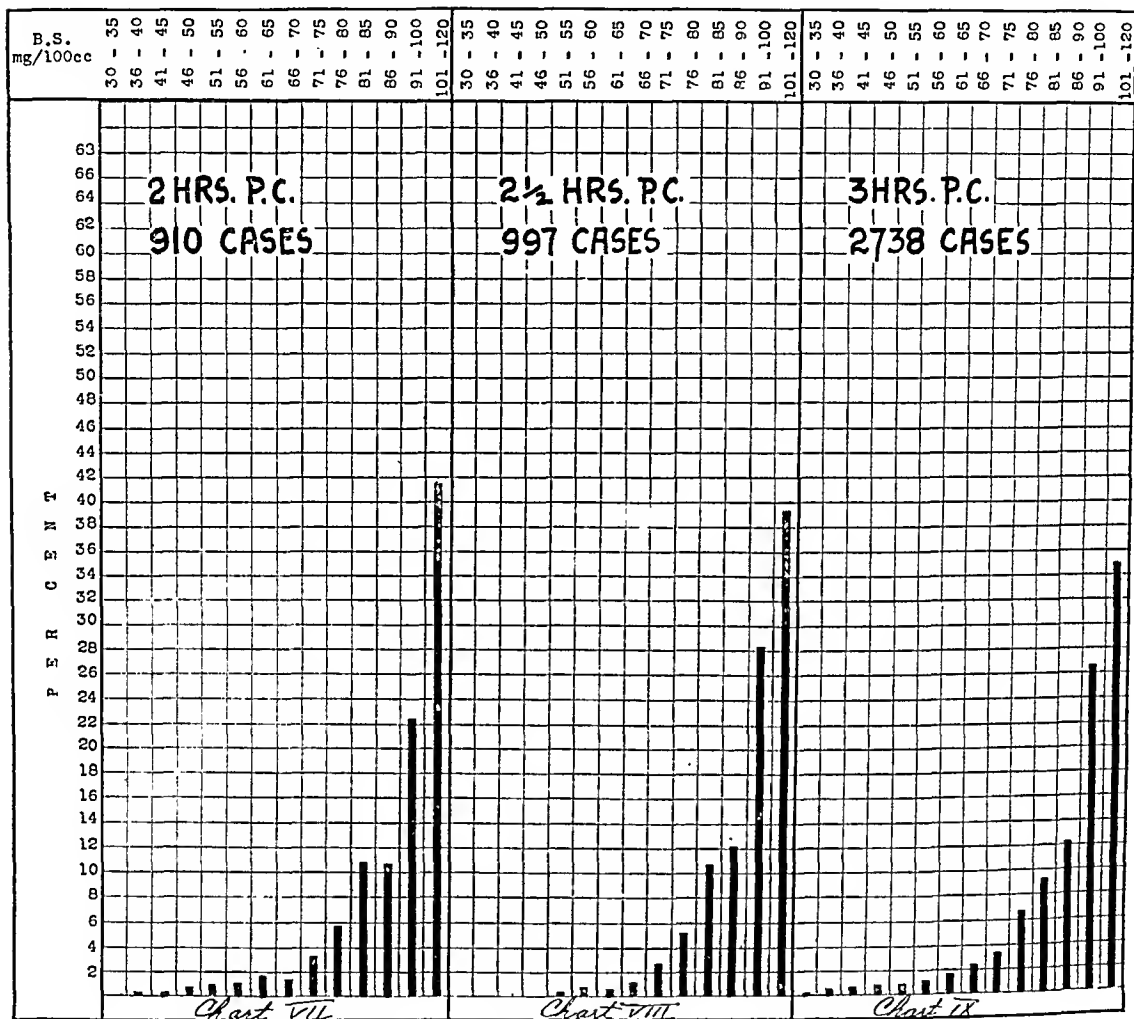
At the end of two and one-half and three hours after the ingestion of glucose this increase in the number of

low values is even more marked. (See Charts VIII and IX). For years I have held the opinion that for the diagnosis of diabetes it is not the fasting blood sugar value that gives the requisite information, but rather the level of the blood sugar two and one-half or three hours after a fairly heavy carbohydrate meal. An estimation of blood sugar during this period helps

one to weed out the early diabetics from the non-diabetics, to distinguish between diabetic glycosuria and non-diabetic glycosuria. During this period—two and one-half to three hours after a meal, a normal individual will present a normal blood sugar no matter

cut to a glucose tolerance curve and has an important clinical application in the differential diagnosis of diabetes.

Charts X to XV represent respectively the blood sugar findings  $3\frac{1}{2}$ , 4,  $4\frac{1}{2}$ , 5, 6, and more than 6 hours after a meal. With the exception of the



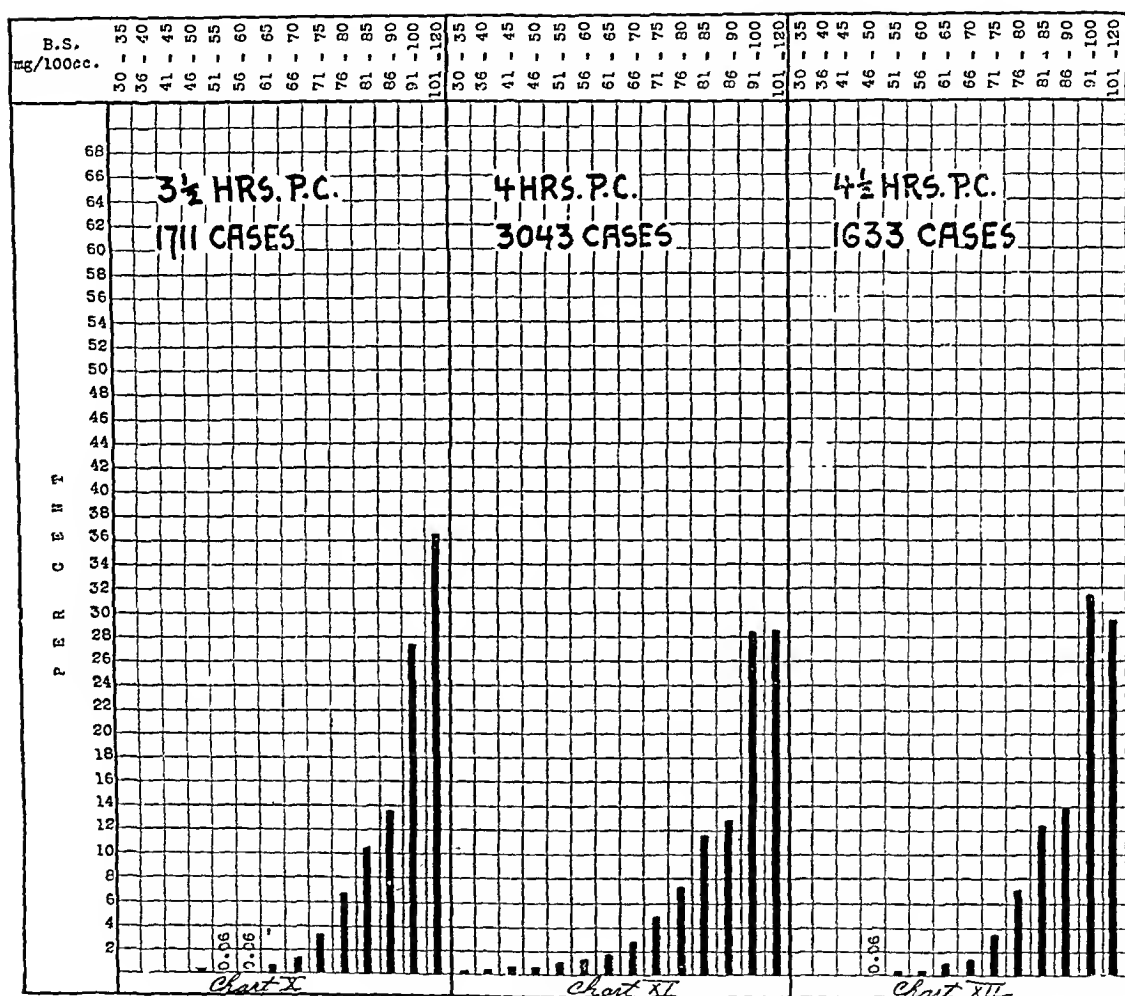
what the carbohydrate content of the meal may have been, whereas a diabetic or a prediabetic individual can not present a normal blood sugar at this time, even though his fasting blood sugar may be within the normal limit. An estimation of the blood sugar two and one-half or three hours after a meal is therefore, so to speak, a short

three and one-half and four hour periods, the blood sugar values for the most part lie between 70 and 120 mg. per 100 c.c., although the first two show quite a few low values, 5.26 per cent lying below 70 mg. per 100 c.c. These observations, which differ so widely from the generally accepted idea regarding the range of normal

fasting and postprandial blood sugar, lead one to consider the mechanism for the initial sugar metabolism.

The blood sugar content is affected by two factors, one of which is exogenous, the other endogenous. The exogenous factor is food, the endog-

give an indication of the exogenous regulation of the blood sugar. The exogenous regulation, on the other hand, is effective principally after more than six hours after the ingestion of food. Of this factor the "fasting" and the "more than six



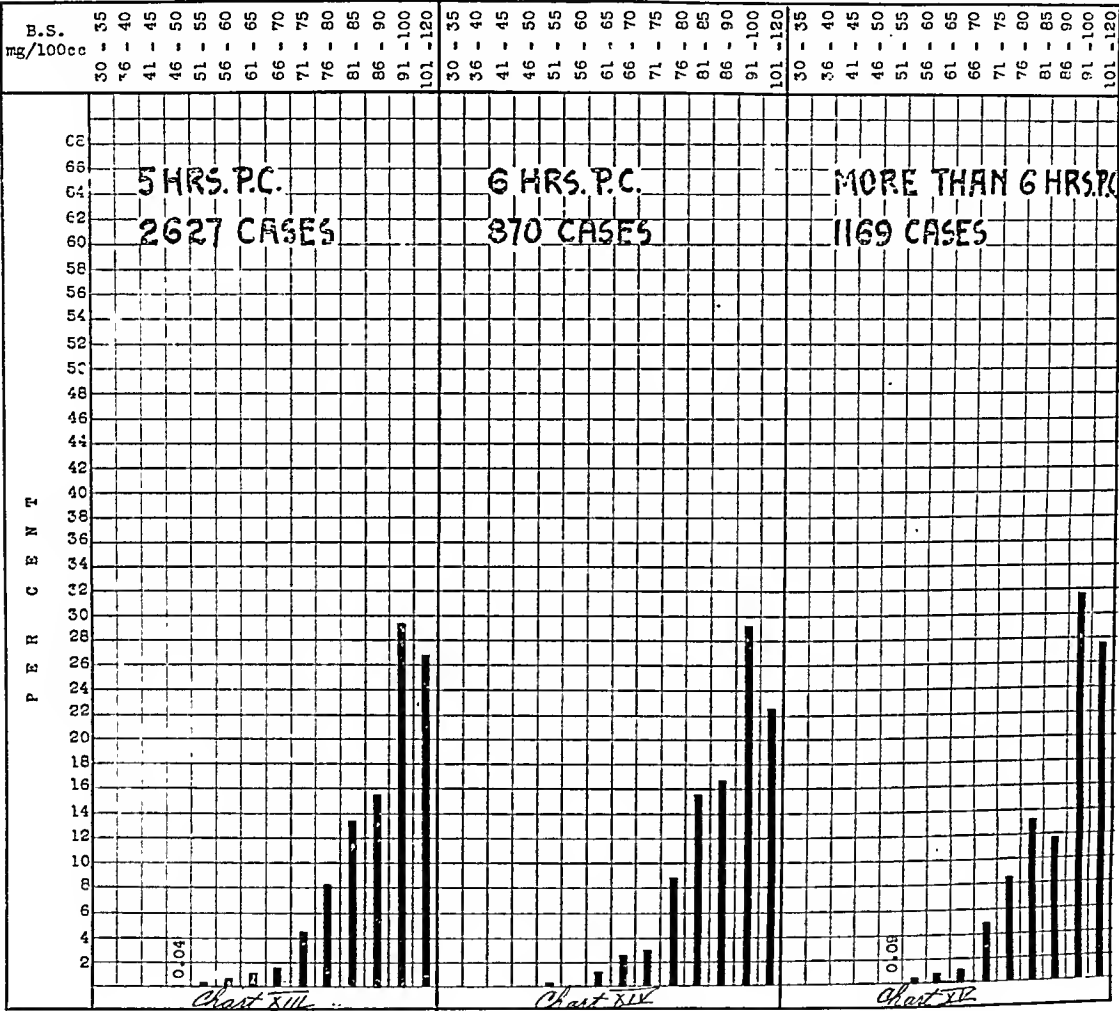
enous factor is the direct transformation of the glycogen in the liver into the glucose or sugar in the blood. All the tissues of the body play a large role in metabolism of the exogenous sugar; the liver is the one effective agent in the storage of glycogen and its transformation into glucose. Thus earlier postprandial estimations really

hours postprandial" blood sugar values are an indication.

There are two chief theories as to the mechanism which keeps the blood sugar within normal limits. First, there is the mechanistic theory which holds that the blood sugar content is maintained by a simple process of diffusion, which presupposes that a like

blood sugar level is maintained in both the liver and the blood. The second is the secretory theory which holds that the blood sugar level is maintained by the secretion by the liver of the necessary amount of glucose into the blood stream. Following a carbohy-

in the blood. One cannot explain the quick removal of the sugar from the blood stream as being due to its consumption and the formation of glycogen, since both of these processes are very slow in their action; and for the proper storage of glycogen insulin



drate meal hyperglycemia ensues, which is quickly balanced by the absorption by the tissues of the excess of sugar from the blood. That this resorption is a vital process is indicated by the varying amounts of sugar in the different organs, the amounts at times even exceeding the concentration

is necessary, as has been shown by Best and others.(3) Perhaps the mechanism for the normal regulation of the blood sugar may best be understood by a study of its derangement which is affected by three factors: 1. the nervous system; 2. the liver; and 3. the insulogenic ap-

paratus. These factors may act directly or indirectly. The direct effects are those in which no definite regulating factor is totally destroyed but in which they are merely deranged (functional effects), so that their total harmonious cooperation is interfered with. The indirect effects are then produced when one of the three regulating factors is destroyed. Thus a diseased condition of the liver will produce directly a derangement of the exogenous factor of the blood sugar regulation; while the extirpation of the liver or poisoning of the liver by phosphorous produces indirectly a derangement of both the exogenous and endogenous factors. On the other hand, stimulation of the sympathetic nervous system will produce hyperglycemia either directly or indirectly as the result of a decreased secretion of adrenalin, which produces the so-called adrenalin hyperglycemia.

Folin and Berglund (4) say that hypoglycemia is probably quite as normal a consequence of carbohydrate ingestion as hyperglycemia, but comes later. "Hypoglycemia is probably a reflection or index of a decreased need for sugar transportation from one set of tissues to another. This condition is obtained when there is an abundance of available carbohydrate material in all the tissues. A general abundance of other suitable food than glucose, notably fat (olive oil) may, therefore, also produce hypoglycemia. Hypoglycemia (in venous blood) can occur even during a prolonged moderate sugar absorption from the intestine, because the absorbed sugar may get by the liver but does not get into the venous blood."

The appearance of hypoglycemia in Marathon runners at the end of the race is a well known fact. Burger and Martens (5) extended similar observations to less strenuous exercises (running for one hour, fencing for 50 minutes, etc.). Two out of seven of the subjects became hypoglycemic, in one the blood sugar dropping from 90 to 61. My own observations do not include any strenuous exercise, outside of walking in a few cases.

The question of adrenalin hyperglycemia has been much discussed in the literature, but I shall quote only the experiments of Ulrich and Rypins (6). These authors administered  $\frac{1}{4}$  c.c. of 1:1000 adrenalin (Parke Davis and Co.) subcutaneously and intravenously. Their results can be summarized as follows:

Average blood sugar, fasting	100 mg. per 100 c.c.
Adrenalin, $\frac{1}{4}$ c.c., 1:1000, injected	
Blood sugar in 15 minutes	114.8 mg. per 100 c.c.
Blood sugar in 30 minutes	103.8 mg. per 100 c.c.
Blood sugar in 60 minutes	99.4 mg. per 100 c.c.

Ambard, Schmidt and Arnovlyevitch (7) have shown that the rate of oxidation of glucose depends on the concentration of insulin as well as of glucose in the blood. The glycemic level also influences oxidation indirectly by increasing the secretion of insulin.

Simon (8) reports a higher level of blood sugar in psoriasis, furunculosis, and eczema, especially in the chronic cases.

In discussing the disappearance of sugar from the blood stream, Cori and Cori (9) conclude from their experiments on animals that an excess of in-



sulin leads to an increased sugar oxidation. According to these authors glucose oxidation and glycogen formation accounted for 90 per cent of the sugar absorbed during four hours in both normal and insulinized animals.

Maranon (10) made glucose tolerance estimations in four cases of progressive muscular atrophy, using only 25 gm. of glucose. In every case the sugar metabolism exhibited a prediabetic lack of balance, the extent of the induced hyperglycemia paralleling that of the atrophic process.

The question as to whether vagus stimulation affects the production of insulin, bringing about a hypoglycemia, is discussed by Clark (11), who concludes that the stimulation of the vagus causes a secretion of insulin which in turn causes hypoglycemia.

Papilian and Jianu (12) produced hyperglycemia by severing both vagi in 10 dogs.

These few citations from the literature are offered merely to indicate the views of certain investigators as to the possible factors concerned in the production of hyper- and hypoglycemia.

### CONCLUSION

An analysis of the 22,808 blood sugar estimations made from the blood of non-diabetic individuals is presented—the blood sugar in each instance has been analyzed as to its height in relation to the length of the postprandial period. The range for normal blood sugar as usually given is from 80 to 180 mg. per 100 c.c. but the present analysis shows that in 2452, or 15.14 per cent of these estimations, the blood sugar is 80 or below; and that in 1791, or 7.85 per cent, it was 75 mg. per 100 c.c. or below, the lowest value being .30 mg. per 100 c.c. Such a high percentage of blood sugar values below 80 mg. per 100 c.c. would indicate that these low blood sugar values are not of rare occurrence. Furthermore that they are apparently normal for these individuals is indicated by the fact that no special complaint is noted in the histories of the cases which I have especially investigated. We used to be alarmed when exogenous insulin lowered the blood sugar below 60 or 65 mg. per 100 c.c. but here is a definite demonstration that endogenous insulin apparently does the same thing, the patient not even being conscious of the low blood sugar content.

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# Tuberculosis of the Gall Bladder\*

BY JAMES T. CASE, *Battle Creek, Michigan*

**T**UBERCULOSIS of the gall-bladder is one of the rarest of pathological findings. The older text-books either make no mention of it at all, or ascribe to it a hypothetical great rarity without any reference to actually observed cases. Although tuberculosis of the liver and of the intrahepatic biliary passages is no great rarity, and although the researches of many writers (Fraenkel and Krause, Joest and Ernshoff, Rabinowitsch, Calmette and Guerin, etc.) have shown the frequent presence of living tubercle bacilli in the bile of the gall-bladder in cases of tuberculosis, both with and without involvement of the liver, the relative great immunity of the mucosa of the gall-bladder to tuberculous lesions has been commented upon many times. The many French observers who were especially interested in tuberculosis of the liver and intrahepatic biliary lesions saw no tuberculous involvement of the gall-bladder in their cases. Veterinary observations confirm the same immunity of the gall-bladder to tuberculous lesions in cases of animal tuberculosis.

The last edition of Aschoff's *Specielle pathologische Anatomie* says that "tuberculosis of the gall-bladder is a rare finding. According to Simmonds two forms exist: A chronic form with

thickening of the wall and chronic ulceration (chronic ulcerative tuberculous cholecystitis), and an acute form in which there are multiple small, bile-stained necroses in the mucosa containing tubercle-bacilli."

Simmonds in 1908 could find in the literature only four published observations on tuberculosis of the gall-bladder, the cases of Heddäus, Schmidt, Kisch and Beitzke.

Heddäus (1894) reported the first case of apparently primary tuberculous cholecystitis, in a married woman of the age of 44 years. For two years she had had violent coughing without expectoration; and for seven months had noticed a swelling in right side, which was not painful but hindered her work. This was opened by her physician and an abundance of pus was discharged. In three weeks the swelling had again appeared in the same place, painless and without other symptoms except sensitiveness on pressure. A fistula developed in the old incision and there was a continuous discharge of pus. On entering the Clinic, her examination showed moderate nutrition, moderate kyphoscoliosis, small goitre, normal lungs and heart, abdomen distended, soft, with many old striae, and separation of recti. In the right hypochondrium below the ribs there was a tumor mass measuring 10x15 cms. The skin was

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movable over this except at the site of the fistula in the mammary line at edge of ribs. The mass moved on respiration. Percussion gave a dull tympanitic tone over it. Temperature on entrance 38.2°, later became normal. Urine negative. Clinical diagnosis of cholecystitis. Operation showed a subcutaneous cavity lined by granulation tissue, communicating by fistula with greatly enlarged gall-bladder. Two tablespoonfuls of caseous pus escaped from the latter on incision. Its cavity was curetted and packed. Microscopic examination of the curettings showed numerous caseous areas with giant-cells throughout the granulation tissue. When seen two years later patient seemed well and felt well save for persistent cough. Fistula had completely healed. Examination of lungs wholly negative.

Schmidt's (1896) case is quoted by Simmonds as being also one of chronic tuberculous ("caseous purulent") cholecystitis with cholelithiasis; but the details of this case are not given, and the reference is not accessible.

Kisch's (1902) case was that of a woman, of the age of 57 years, suffering from *paranoia chronica* and *tabes*, with optic atrophy of 13 years duration. Eight days before death she developed fever and pulmonary symptoms. There was no suspicion of gall-bladder disease. The clinical diagnosis was bilateral croupous pneumonia. Autopsy showed a chronic pulmonary tuberculosis, tuberculosis of the bronchial nodes, old tuberculous pericarditis, tuberculous ulcers in ileum, and chronic tubercles in liver, spleen and kidneys. The gall-bladder was adherent to neighboring structures and com-

municated by a small perforation with the colon. Its cavity was filled with gall-stones, 24 in number, about the size of peas, and with thick yellowish pus. The mucosa of the bladder was converted throughout into caseous masses, 4-5 mm. thick. Towards the serosa the caseous zone changed into a grayish translucent tissue; on the liver side the caseous masses invaded the liver in foci, many of which were as large as hazel-nuts. The distal fourth of the cystic duct showed the same appearances of caseation. In a distended portion of the duct there was a pea-sized stone. The hepatic and common ducts appeared normal, and contained apparently normal bile. No tuberculous lesions were found in the stomach, duodenum or jejunum. The microscopic examination of the gall-bladder wall showed a typical picture of tuberculous caseation, epithelioid tissue and giant-cells, with numerous tubercle bacilli in the lesions. No bacilli were found in the pus contained within the cavity of the gall-bladder. Kisch regarded the process as chronic and most probably the result of a haematogenous metastasis of tubercle-bacilli, excreted through the liver into the bile, and giving rise to the tuberculous infection of the gall-bladder mucosa as a result of its lessened resistance due to the gall-stones and the blocking of the cystic duct.

Beitzke's case (1905) was that of a 57 year old male, dying of tuberculous meningitis and general miliary tuberculosis. The autopsy showed in addition extensive caseation of left testis and epididymis, seminal vesicles and prostate, calcified bronchial and mesenteric nodes, old fibroid apical tubercu-

losis on the right, and scattered intestinal ulcers. The gall-bladder was of the size of a goose-egg; its external surface tense and shining like tendon; its cavity distended. On opening it was found full of a yellowish-green pus-like fluid. In the entrance into the cystic duct there was a hard pigment stone about the size of a cherry. The gall-bladder wall was several mm. thick, thickly beset with miliary gray to grayish-yellow nodules, giving it a shagreened appearance. Only in a few spots was the mucosa visible, but in such places it had lost its velvety appearance, and was either smooth or showed fine scar-like folds of a grayish color. There was no imbibition of bile. The microscopic examination showed that the mucosa was almost completely destroyed by the nodules and replaced by tuberculous granulation tissue which infiltrated the whole submucosa, and extended deep into the muscularis, interrupting it in places. The increased thickness of the wall was due chiefly to the thickening of the submucosa which constituted about two-thirds of the entire wall. It consisted of dense fibrous connective tissue without tubercles. The contents of the bladder were not pus, but consisted chiefly of amorphous mucoid masses with a few epithelial cells and leucocytes. Occasional tubercle-bacilli were found in smears made from it. Since tubercle bacilli have been found frequently in human bile without accompanying lesions of the gall bladder, Beitzke thinks that there must be some especial predisposing factor in the production of gall-bladder tuberculosis, and this he finds in the chronic cholecystitis and cholelithiasis. He

regarded his case as due, not to the recent miliary tuberculosis, but to an occasional hematogenous metastasis to the liver and excretion into the bile of tubercle bacilli entering the blood from the severe tuberculous lesions of the genital tract. The only other case of gall-bladder tuberculosis that Beitzke could find in the literature was the one of Kisch. He quotes Kauffmann as saying that tuberculosis of the gall bladder is very rare, but that it may lead to the production of round, saccular or stellate ulcers that, extending through the wall, may lead to perforation. This statement likewise may be traced back to Kisch's case which showed a perforation into the colon.

In Simmonds' first article (1908) he calls attention to the extreme rarity of tuberculous lesions of the gall-bladder in spite of the fact that tuberculosis of the liver and intra-hepatic biliary passages is not rare, and that tubercle bacilli are frequently present in the bile. He could find in the literature only the four cases of Heddäus, Kisch, Schmidt and Beitzke mentioned above, all four of these cases presenting a severe caseous purulent cholecystitis with stone-formation. Acute miliary tuberculosis of the gall-bladder was not yet known. He reports a case of the latter condition in a nine-months old child showing countless miliary tubercles, bile-stained necroses and degeneration cysts in the liver. There was a generalized miliary tuberculosis of all organs, caseous bronchial and mesenteric glands, and tuberculous ulcers in ileum and colon. The gall-bladder was of normal size and the contents appeared normal. No tubercle-bacilli could be found in the latter. In the otherwise

normal-appearing mucosa there were six flat, sharply circumscribed areas, of the size of lentils, showing a marked bile-imbibition. Microscopical examination showed these to be areas of necrosis surrounded by a zone of granulation tissues. No tubercles or giant-cells were present, but the necrotic areas contained great numbers of tubercle bacilli at the border of the granulation tissue and caseous material. No tubercle bacilli were found in any other part of the gall-bladder wall. Simmonds believed the gall-bladder tuberculosis in this case to be wholly comparable with the excretory tuberculosis of the kidney-pelvis, tubercle bacilli passing into the intrahepatic bile-ducts and into the bile. Two forms of tuberculosis of the gall-bladder may result, a chronic ulcerative cholecystitis and the acute miliary tuberculous necroses of the mucosa.

Simmonds' case was presented before the meeting of the biologic section at Hamburg, in 1908, and in the discussion which followed, Deycke described a case which he personally had seen of empyema of the gall-bladder with a stone in the cystic duct. Animal inoculations showed the pus to contain tubercle bacilli, although cultures were sterile, and the microscopical examination showed diffuse tuberculous lesions in the mucosa.

Later Simmonds presented a second case of gall-bladder tuberculosis occurring in an 11 year-old child whose liver was thickly studded with tubercles and showed advanced tuberculosis of the intra-hepatic biliary passages. The mucosa of the gall-bladder contained numerous minute greenish sloughs of tuberculous necrosis containing tuber-

cle bacilli. Simmonds regarded this case as a second one of excretory infection of the gall-bladder mucosa.

In his report of this second case, Simmonds adds another case of gall-bladder tuberculosis from the literature that of Knotte, 1907, who observed a tuberculous cholecystitis in a severe case of generalized tuberculosis. Knotte regarded a pre-existing cholecystitis as significant for the later tuberculous invasion. Cholelithiasis was not present in this case.

These eight cases of tuberculosis of the gall-bladder are the only ones that the writer has been able to find in an extensive survey of the German literature. While the French have given much attention to the study of tuberculosis of the liver and of the intraphepatic bile ducts, the great majority of the writers on these subjects make no mention of the gall-bladder. There exists one possible French case in the older literature, that of Gaucher (1870) who describes a case of tuberculosis of the liver in a child of three years of age, showing tuberculosis of lungs, pleurae, kidneys, spleen, mediastinal glands and intestines. In the liver the tubercles were arranged along the bile-passages, while in the gall-bladder there was a "tuberculous mass as large as a hazel-nut." While the tuberculous nature of this lesion cannot be accepted as beyond all doubt, it may be regarded as a probable case.

The case reported by Lancereau is also a doubtful one, as the diagnosis is based upon gross appearances only. In an autopsy upon a woman thirty-two years of age a caseous mass replacing the gall-bladder was found. What were regarded as tuberculous granula-

tions were seen in the common duct and many "tubercles" were present in the spleen and mesenteric glands, and there was necrosis of a portion of the pubis. Lancereau regarded this case as one of primary tuberculosis of the gall-bladder.

In 1910, Galabrée reported two cases of tuberculous cholecystitis. The first case is doubtful, as no microscopic examination was made, and the gross pathological changes in the gall-bladder are very misleading. The second case is acceptable, as histologic examination of the thickened wall of the gall-bladder revealed many tubercles and tubercle bacilli. The patient was a woman, thirty-nine years of age, who had previously been perfectly well. For a month she had continuous sharp pain in the right side, increasing a few minutes after eating. There was a large abdominal tumor in the upper right side which was diagnosed as a kidney tumor. Posterior incision showed a normal kidney. Incision through the upper right rectus was made and the tumor was found to be transfixing gall-bladder containing one perforating stone and pus.

In 1911, Latronche collected four cases of supposed tuberculous cholecystitis and added one of his own. As only two of these cases had a microscopical examination, and as only in one were positive tubercles found,—that of Latronche, in which the tubercles were in the serosa of the gall-bladder as a part of a tuberculous peritonitis,—all of these cases can be excluded. The presence of a caseous pus in the gall-bladder is a very common event in old cases of empyema of this organ, and the fact that the pus ap-

pears caseous in character does not by any means stamp it positively as tuberculous in origin.

The only American cases of tuberculosis of the gall-bladder so far reported have been a preliminary report of the present case (the first American case) in the Transactions of the Western Surgical Association for 1925. In the Annals of Surgery for 1926, Rankin and Massie reported a case which they regarded as one of primary tuberculosis. The patient, a negress, aged thirty-eight, complained of pain and a mass in the right upper quadrant of the abdomen. History of pulmonary tuberculosis seven years ago. Clinical diagnosis of perforated duodenal ulcer with abscess formation. At operation a large mass was found adherent to liver and small intestine. When opened this was found to be the gall-bladder with walls about three-quarters of an inch thick, containing caseous pus but no stones. Microscopically, sections from the gall-bladder showed marked hyaline connective tissue thickening with dense infiltrations of lymphocytes and plasma cells, with a number of areas of necrosis surrounded by endotheloid and lymphoid cells with a few giant cells. Four years after the patient returned, showing shortness of breath, ascites and edema of feet. Clinical diagnosis was tuberculous peritonitis. Operation revealed abundant fluid in abdomen and peritoneum studded with tubercles. Although the microscopical description is not wholly convincing, this case is most probably one of gall-bladder tuberculosis, but the history and the association of an advanced generalized peritoneal tuberculosis make it doubtful that the gall-

bladder was the primary focus of the disease.

Rankin and Massie in reporting their case state that their search of the literature reveals only fifteen reported cases of primary tuberculosis of the gall-bladder. They include, however, the cases of Lancereau, the first case of Galabrée, the four cases (Broquehave, Tedenat, Riedel and Czerny) collected by Latronche, and the latter's own case, all of which we reject on the ground of insufficient evidence of the tuberculous character of the affection, or because the tuberculosis was evidently primarily peritoneal. This would reduce the number of reported cases of gall-bladder tuberculosis to eight undoubted cases (Heddäus, Schmidt, Kisch, Beitzke, Knotte, Simmonds, Deycke and Simmonds) at the time the preliminary report of our case was made in 1925. Counting these together and adding the case since reported by Rankin and Massie there are in the literature only ten reported cases of primary gall-bladder tuberculosis.

Since our case, the first one reported in America, has been published only in the Transactions of a limited society, it has seemed desirable to republish it here in fuller form, particularly since it had been missed in the survey of the literature given by Rankin and Massie.

#### *Author's Case*

Case No. 168-314—Female, age 59, housewife, referred to one of us (J. T. C.) by Dr. N. E. Knapp. Family history negative for tuberculosis. The patient suffered from spinal meningitis at the age of eighteen, followed by inflammatory rheumatism. There is a tendency to bronchitis, for which the patient has taken serum. Typhoid fever twice: first time thirty years ago, second time twenty years ago, followed by furuncu-

losis. Operation for bad lacerations following childbirth. Peritonitis a few months later. Attacks of chronic appendicitis but no operation. Complete hysterectomy fifteen years ago for uterine fibroid. Severe headaches from puberty to menopause.

*Summary of present ailment:* Attacks of severe pain in epigastrium during the last year. Last attack followed by extreme exhaustion. The pain seldom extended to the right side but was accompanied by aching in the left upper abdomen, especially posteriorly, with the later attacks. The epigastric soreness was present more or less all the time, but was aggravated by movement, such as walking, or turning over in bed. Pain and stiffness in right knee, pain radiating to hip. Looseness of bowels, amounting at times to diarrhea. Soreness in rectum on bowel movement. Occasional stabbing pain in precordial region. Some palpitation and shortness of breath. Fatigue. Overweight, but has noted a loss of seventeen pounds during the last year.

*Summary of Physical Examination:* Height 62.1 inches. Weight 164 pounds. Temperature 98.4° F. Pulse 72, reclining. Blood pressure: systolic 135, diastolic 85. Rather heavy frame. Overweight. Muscles rather flabby. Joints not swollen. Crepitation in right knee. Skin and mucous membranes a trifle pallid. No enlarged glands palpable. Pupils react promptly to light. Tongue slightly coated. Chronic pharyngitis. Pyorrhea. Tonsils removed. Chest well developed, and expansion good. Breasts normal. Lungs normally resonant. Respiratory sounds normal except for some harsh breathing at the bases. No pulmonary congestion. No definite râles. The apex beat neither seen nor felt. Cardiac diameter 9.5 cm. to the left, but does not extend beyond the right sternal border. Heart sounds fairly distinct. No edema of lower limbs. Liver dullness normal. Splenic dullness not increased. Epigastric percussion and palpation gave considerable discomfort. Marked abdominal tenderness.

*X-ray Examination with Opaque Meal:* Stomach normal as to function and appear-



ance, except for moderate delay in the emptying time (a quarter of the meal remaining at the sixth hour). No abnormality in small intestine. Multiple diverticula of colon, especially the pelvic loop, but without indications of colonic obstruction.

*Laboratory Findings:* Urine normal.

Blood: Hemoglobin 87. Red cells 4,630,000. White cells, 5,100. No differential bloodcount made. Non-protein nitrogen 31.1. Uric acid 4.0. Blood sugar 110. Alveolar  $\text{CO}_2$  tension 33.

Fecal examination showed a bad flora predominating but no other unusual findings.

Gastric juice analysis: Considerable bile in gastric contents. Marked hyperacidity, both total and relative.

*Surgical Consultation:* Resulted in a definite diagnosis of chronic gall bladder disease with gall stones and a recommendation for operation.

*Operation:* July 18, 1924 (by J. T. C.) in the Hospital of the Battle Creek Sanitarium. The gall bladder was found buried in adhesions, very dense in character and separated only with the greatest difficulty. The adhesions involved all the neighboring structures. The liver appeared smooth and normal except for the pericholecystic adhesions. The gall bladder, which contained one large stone the size of a pigeon's egg, besides a soft indeterminate mass in the fundus, was removed with as wide dissection as possible including a part of the liver substance, and a drain was tied into the cystic duct. The stomach and duodenum seemed normal, except for the adhesions. No stones were palpable in the common duct. Pancreas normal to palpation.

When the gall bladder was opened, there was found within it a friable degenerating mass which strengthened our already strong suspicion of a malignant process.

The postoperative convalescence was stormy. The temperature reached as high as  $103^{\circ}$  on the second day and remained high for two more days. There was a very free drainage of bile-stained material from the wound and the dressings had to be changed frequently. On the sixth day the drainage

material looked so much like duodenal contents that we made a test by giving the patient in the morning capsules containing carmine; in the evening there was carmine on the gauze dressings, thus making sure a diagnosis of duodenal fistula. The patient's temperature dropped to normal on the seventh day and remained approximately normal during the remainder of the convalescence. The skin was protected with animal charcoal, a treatment which later caused trouble; for many months after the operation an abscess developed in the abdominal wall which cleared up promptly after the evacuation of pus and a quantity of charcoal. The stool was free from bile on repeated tests.

During the next ten days the patient at times developed a condition of mental confusion, urinary retention and irregular pulse, which made us despair of her recovery, but under repeated intravenous injections of glucose and Ringer's solution these symptoms passed.

Every device for closing the duodenal fistula failed, including the application of constant suction of the excoriating juices from the wound. The passage of a duodenal tube was proposed but only on the twenty-first day did the patient finally consent. An ordinary duodenal tube was then passed through the stomach and duodenum well into the upper jejunum. The drainage through the fistula at once diminished, and ceased almost entirely within seventy-two hours. On the fourth and fifth days the wound was absolutely dry when dressed, all skin irritation having subsided. Nausea and other unfavorable symptoms were absent, except that once or twice daily, following the introduction of the duodenal tube, the discomfort of the tube caused the patient to vomit a little bile, this being the first time that bile had passed into the duodenum. The presence of the tube disturbed the patient so much that nausea began to reappear, so that on the thirtieth day after the operation, nine days after its introduction, the duodenal tube was removed. From then on the patient's recovery was uneventful.

Let us remark here, in connection with the duodenal fistula, that introduction of the duo-

denal tube within a day or two of the diagnosis of duodenal fistula would undoubtedly have shortened this patient's convalescence by at least 100 per cent and made unnecessary a later operation for abdominal hernia. The value of the duodenal tube lying well into the upper jejunum in this type of case is analogous to the usefulness of an inlying catheter in an immediate after-care of cases of vesico-vaginal or other forms of vesical fistula. The literature contains little mention of this means of treatment for duodenal fistula, two cases by Einhorn and one or two others being the only ones available in a cursory search of the literature.

A letter from the husband sixteen months after the operation reported that the patient's general health was good and that there had been no return of the abdominal symptoms.

The *pathologist's report* (A. S. W.) on the specimen removed (U. of M. No. 301-AC) follows:

Gallbladder: Small with greatly thickened wall, containing a large, oval, pigment and cholesterin calculus. At the mouth of the gall-bladder the cavity is completely obliterated by a mass the size of a hickory nut. The cystic duct is likewise very much thickened and partly obliterated. Besides the stone, the cavity of the gall-bladder contains caseous pus.

Microscopic examination: Mucosa almost entirely replaced by caseating tubercles. Only toward the neck of the bladder are there any remains of the glands of the mucosa. The greater part of the mucosa of the fundus consists of a caseating tuberculous ulcer. Throughout the entire wall are scattered caseating miliary tubercles. In some areas the tuberculosis of the mucosa extends deep into the wall, forming deep fistulous tracts, lined with caseous epithelioid tissue. Giant cells are numerous in the smaller tubercles.

Toward the neck of the bladder portions of the glandular mucosa are preserved showing numerous tubercles arising in the mucosa between the glands. The muscularis and subserosa of the bladder wall show marked fibrosis, and a few small miliary tubercles are found in the subserosa—none on the peritoneal surface. The process diminishes in intensity from the mucosa towards the serosa.

*Pathological Diagnosis:* Chronic tuberculosis of the gall-bladder. Chronic tuberculous cholecystitis.

#### COMMENT

The eight older cases fall into the two groups of the classification proposed by Simmonds and accepted by Aschoff:

Chronic tuberculous cholecystitis. .6,  
4 of these with cholelithiasis.

Acute miliary tuberculous necrosis ..... 2

Our case was one of chronic tuberculous cholecystitis associated with cholelithiasis; that of Rankin and Masie was the same without any calculus. Five of the eight cases then of chronic tuberculous cholecystitis were associated with cholelithiasis; three were not. From this association the presence of calculi can hardly be regarded as significant in lowering the gall-bladder resistance to tubercle bacilli entering through the bile. The calculi may be either primary or secondary to the infection, and it is impossible from the data at hand to say which. There is nothing distinctive in the symptomatology of gall-bladder tuberculosis, and it is very unlikely to be recognized clinically when it is primary and confined to the gall-bladder. Its diagnosis will rest wholly upon the



FIGURE 1. Low power of gall-bladder wall, showing base of tuberculous ulcer of mucosa. Caseating border of epithelioid tubercles.

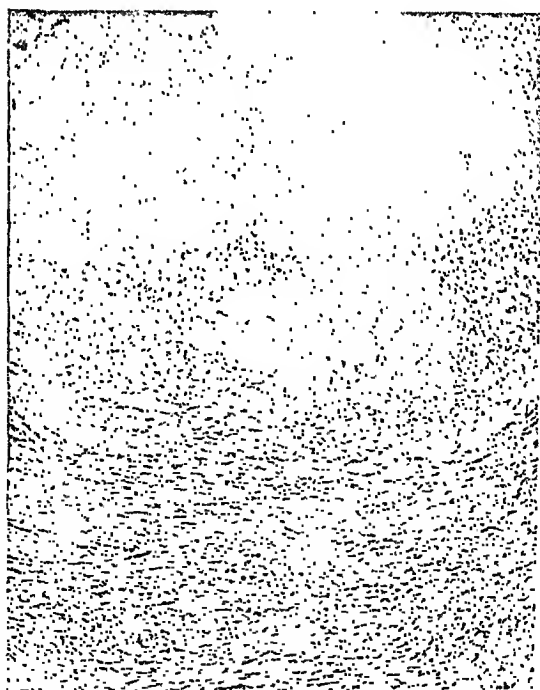


FIGURE 2. Low power of gall-bladder wall, showing caseous ulceration of epithelioid tubercles replacing the mucosa.

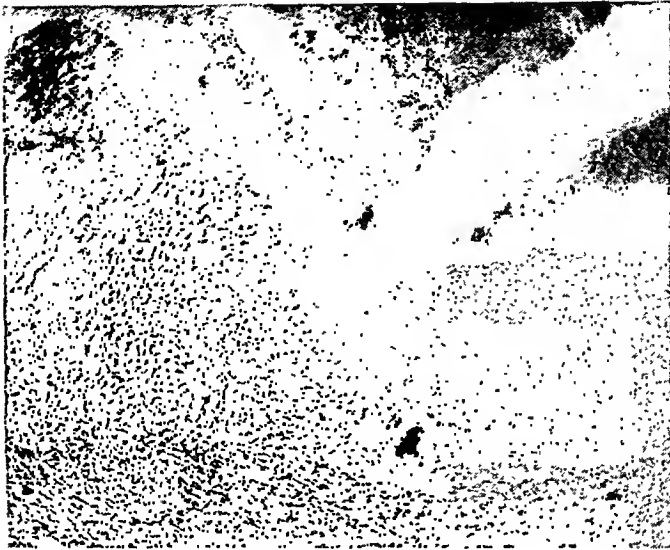


FIGURE 3. Higher power of caseous ulcer of mucosa of gall-bladder. Epithelioid zone with giant cell.

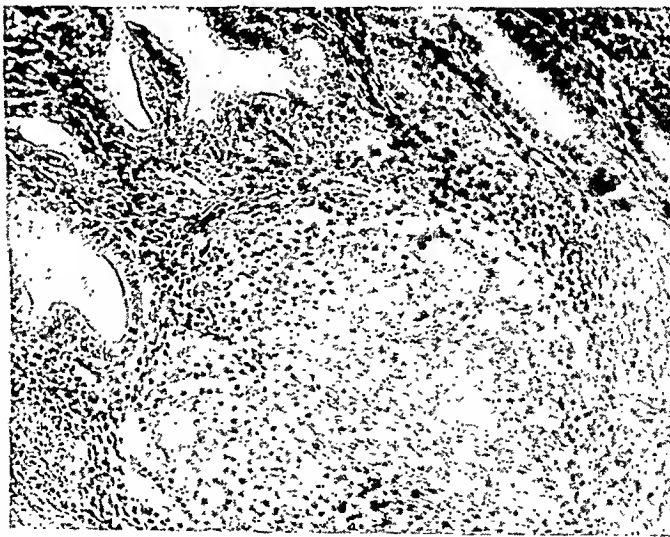


FIGURE 4. Non-ulcerated portion of gall-bladder mucosa showing epithelioid tubercles in stroma of glands.



FIGURE 5. Miliary tubercles in gall-bladder mucosa.

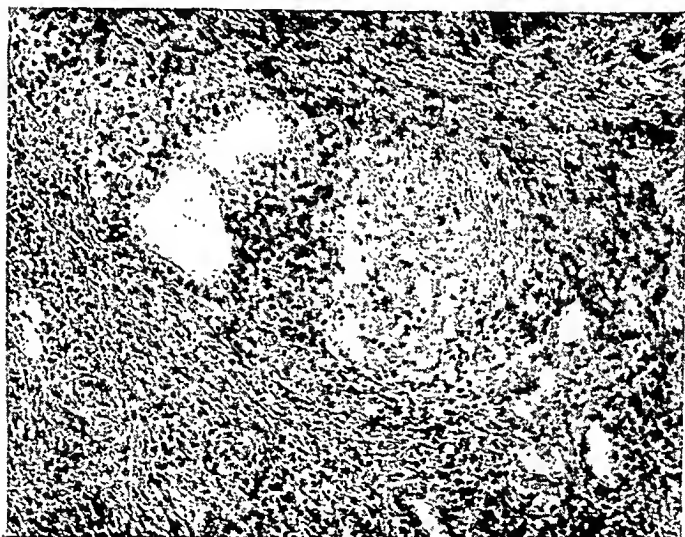


FIGURE 6. Higher power view of miliary tubercle in gall-bladder mucosa with atrophy of mucosa.

findings of the pathologist, and the condition because of its extreme rarity must be regarded as a pathological curiosity. The most interesting point about it is the theoretical explanation of its rarity. Why does the gall-bladder escape tuberculous infection to so much greater extent than the pelvis of the kidney, for example? All of the evidence points to a high degree of immunity to the tubercle bacillus on the part of the gall-bladder mucosa. The relationship of the bile itself to this immunity is a factor to be considered, but we do know that tubercle bacilli contained in bile do not lose their virulence in animal experimentations. Rankin and Massie say that all of the reported cases have been in females; this is an error, as Beitzke's case (1905) was that of a 57-year-old male. It is very probable that all of the cases of gall-bladder tuberculosis are associated with tuberculous lesions, either active or latent, elsewhere in the body, and that the involvement of the inter-

ior of the gall-bladder is of the nature of an excretory infection by way of the biliary passages. The possible involvement of the peritoneum in all cases of gall-bladder tuberculosis must be always borne in mind. As to treatment, cholecystotomy should be performed in any case in which, at operation, a suspicion of gall-bladder tuberculosis arises.

### *Conclusions*

Tuberculosis of the gall-bladder is a very rare affection. It has no clinical entity, and cannot be differentiated clinically from other forms of cholecystitis. Its diagnosis rests wholly upon the pathological examination. The mucosa of the gall-bladder possesses a very high degree of immunity against infection by the tubercle bacillus. When such an infection does occur it is probably always an excretory infection, by way of the bile, of bacilli arising from some other tuberculous focus, latent or active, within the body.

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# O-iodoxybenzoic Acid in the Treatment of Infectious Arthritis; Report of Eighty Additional Cases\*

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**I**N a previous communication (1) A. G. Young and the author reported the results obtained in a series of forty-three patients with infectious arthritis treated with O-iodoxybenzoic acid. Since then Smith (2) has reported his results with the drug in a series of thirty-three patients. The present paper is a study of eighty additional cases treated at the University Hospital since the first report and includes all patients who have been under observation for a period sufficiently long to warrant an estimate of the amount of improvement gained. All of them have been under observation for a period of at least six months; thirty-three have been under observation for a year or more.

In some important respects the present series differs from that of the first report. The patients included in this series are not a group selected, treated and studied solely by the author. Instead the group includes patients of various members of the staff, selected by them in the ordinary course of practice for the treatments. To a large extent the patients were not treated

personally by the author but received their treatments in the clinic under the author's supervision, a special treatment clinic having been established for that purpose. Such a procedure was made necessary by the large number of patients to be treated and while to some extent it influences unfavorably the results of treatment, because of the lessened personal attention given individual patients, it gives a more uniform estimate of the improvement generally to be expected as the result of treatment under average circumstances. Also, under this arrangement the estimate of improvement gained has been based to a considerable degree on the opinions of more disinterested observers.

The distribution of the cases in respect to age, duration of disease, degree of crippling or deformity and type of arthritis is shown in Tables II to V inclusive. As in the previous report the extent of deformity or crippling has been based on the amount and kind of relatively permanent change present such as bony or fibrous ankylosis, subluxations, muscular atrophy, tendon and muscle contractions and the like, not on the basis of deformity or loss of function due to pain,

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swelling, tenderness, muscle spasm, etc. The classification of the various forms of arthritis has been based on the usual diagnostic criteria including the roentgenologic findings. In classifying the various forms of arthritis the author has considered the degenerative (hypertrophic) form to be infectious, at least in part. The presence of both degenerative and proliferative (hypertrophic and atrophic) changes in the same patient, to which further reference will be made later, has to some extent influenced this decision.

#### METHOD OF TREATMENT

The method of treatment was in general the same as that previously employed. However, not all the patients were hospitalized, a large number being treated as ambulatory patients in the Out-Patient Department in the special treatment clinic mentioned above. O-iodoxybenzoic acid in the form of the ammonium salt (ammonium iodoxybenzoate) was given intravenously in doses of one gram in one per cent solution (100 cc. of a one per cent solution). The drug was prepared by dissolving it in warm, sterile, freshly distilled water. For convenience in treating a large number of patients the total amount to be used in one day was prepared in bulk and generally passed through a Berkefeld filter. Single doses were prepared by simply dissolving the drug in the proper amount of water as described above. As stated in the former paper the solution should not be boiled and should be used within two hours after being prepared. It was administered intravenously, at body temperature, by the gravity method over a period of seven

minutes or more, following the precautions usually observed in intravenous therapy.

Treatments were given twice a week, six to ten treatments (generally eight) constituting a "course." Ordinarily from one to three courses were given with intervals of from two to eight weeks between courses, but in some instances longer periods of time were allowed to elapse between courses because of the failure of patients to return on time. In a few instances less than one course of treatment was given. Three patients received three or more courses. Two of the latter were treated partly by means of rectal administration. For administration by rectum doses of two grams in two per cent solution were employed, the courses consisting of ten to twelve injections.

Some of the patients received treatment other than the drug. For the most part this consisted of baking and massage, but two patients were treated with diathermy and one received sufficient thyroid extract to raise the basal metabolism to normal and hold it at that level. In practically every instance this supplemental treatment was used in such a way as to permit a separate estimate of the amount of improvement secured by it. Generally speaking this treatment was insufficient in amount to influence the course of the disease. Prophylactic orthopedic measures which were freely used for the prevention of deformities are not classified with these other forms of therapy. Orthopedic treatment for the relief of deformities was employed in some cases in connection with the use of O-iodoxybenzoic acid but in



such a manner as to allow easy distinction between the relief obtained by it and by the drug. Reference is made elsewhere to this combined use of orthopedic surgery and O-iodoxybenzoic acid.

The greater number of the patients treated had had all obvious foci of infection removed before coming under our care. In the case of those who had not, such apparent foci were removed and the effect observed preliminary to treatment with the drug. Those patients confined to the hospital received simple medical care and their activity was governed by the extent of their disability. Active motion was encouraged. Analgesics, which were sometimes required at the beginning of treatment, quickly became unnecessary in the successful cases. Most of the patients had previously been treated adequately or inadequately by a variety of methods.

### RESULTS

The results in general are summarized in Table I. It is seen that of the entire 80 cases, 45 or 56 per cent were markedly improved, 13 or 16 per cent, moderately improved, 10 or 13 per cent, slightly improved, and 12 or 15 per cent, were unimproved.

TABLE I.  
TREATMENT WITH O-IODOXYBENZOIC ACID.  
SUMMARY OF RESULTS.

Improvement	No. of Cases	Per Cent
Marked .....	45	56
Moderate .....	13	16
Slight .....	10	13
None .....	12	15
Total....	80	100

As in the previous report the amount of improvement is gauged by the re-

sults in each individual case since improvement is entirely a relative factor depending on the circumstances in each separate patient. Obviously, loss of pain and partial restoration of function in a helpless cripple is a much greater improvement for him than for one who already possesses a considerable degree of functional integrity. As in the first series reported improvement has been taken to mean loss or diminution in pain, swelling and tenderness, increased function and improvement in general health.

The degree of improvement as related to the various groups as classified is shown in Tables II to V inclusive. Table VI shows the relation of improvement to the amount of treatment received.

TABLE II.

TREATMENT WITH O-IODOXYBENZOIC ACID.  
AGE OF PATIENTS AND RELATION TO IMPROVEMENT GAINED

Age Groups	No. of Cases	Improvement				
		Marked	Moderate	Slight	None	
10-19	6	5		1		
20-29	25	15	2	5	3	
30-39	19	12	3		4	
40-49	20	10	6	2	2	
50-59	7	3	1	1	2	
60-69	3		1	1	1	
Total	80	45	13	10	12	

### DISCUSSION

An analysis of the kind of improvement received is of value and may have a bearing on the action of the drug in this disease. Relief of pain continues to be the most common and outstand-

TABLE III.

TREATMENT WITH O-IODOXYBENZOIC ACID.  
AMOUNT OF CRIPPLING AND RELATION TO  
IMPROVEMENT GAINED

Crippling	No. of Cases	Improvement			
		Marked	Moderate	Slight.	None
None ....	23	17	2	1	3
Slight ...	25	14	3	4	4
Moderate	22	11	6	2	3
Marked...	10	3	2	3	2
Total	80	45	13	10	12

TABLE IV.

TREATMENT WITH O-IODOXYBENZOIC ACID.  
DURATION OF DISEASE AND RELATION TO  
IMPROVEMENT

Duration of Disease	No. of Cases	Improvement			
		Marked	Moderate	Slight.	None
Acute .....	9	8			1
6 mo. to 1 yr.	10	4	3	1	2
1 to 2 yrs. .	14	9	1	2	2
2 to 5 yrs. .	27	16	6	2	3
5 to 10 yrs. .	8	2	1	2	3
Over 10 yrs. .	12	6	2	3	1
Total	80	45	13	10	12

TABLE V.

TREATMENT WITH O-IODOXYBENZOIC ACID.  
TYPE OF ARTHRITIS AND RELATION TO IM-  
PROVEMENT

No. of Cases	Type of Arthritis	Improvement			
		Marked	Moderate.	Slight	None.
Simple (acute) ..	8(*)	6	2		
Gonorrhoeal.....	9(*)	6		2	1
Hypertrophic..	15(****)	7	3	2	3
Atrophic.....	54(****)	29	10	6	9
	86				
Duplicate	6				
Total	80				

\*Duplicate (Mixed) Cases.

TABLE VI.

TREATMENT WITH O-IODOXYBENZOIC ACID.  
AMOUNT OF TREATMENT AND RELATION TO  
IMPROVEMENT.

Amount of Treatment	No. of Cases	Improvement			
		Marked	Moderate	Slight	None
Less than one Course	8	2	1	1	4
One Course .....	33	20	3	4	6
Two Courses .....	36	21	8	5	2
Three or more Courses .....	3	2	1		
Total .....	80	45	13	10	12

ing result secured. In a large majority of the patients receiving improvement the great decrease or disappearance of pain, which in many cases had been present for years, constituted the most outstanding relief obtained. Even in those cases in which only partial improvement occurred relief from pain was frequently secured. So frequent and marked has been this effect that it alone in some cases has been considered adequate justification for the

use of the drug, and in some instances it was employed for this purpose even though there seemed little likelihood of any other improvement.

In addition to relief of pain the increase in function, principally increased range of motion, was frequently striking. As previously noticed, such increase in function in patients consid-

ered to have quite permanent fixations and deformities suggests that such fixations and deformities are not infrequently less permanent than they apparently seem. Increased function due to relief of pain, swelling, effusion, muscular spasm and tenderness were naturally still more frequently encountered.

Of particular interest has been the improvement in the general health. This was manifested not only by the disappearance of fever and other signs of infection but especially by a gain in weight, increased appetite, improved color, and by a feeling of general well being and a changed mental attitude. An increase in weight during and following treatment was a nearly constant feature of the improvement. Further evidence of improvement in the general health was noted in the disappearance of trophic changes in the skin, nails and hair, reestablishment of menstruation and loss of muscle atrophy. With the latter there was an increase in strength and an improvement in function which was in turn itself responsible for an increase in muscle strength and tone. The observation of these changes has suggested to the author that they are not due solely to the disappearance of the infection but to a definite action of the drug.

Attention should be called to the advantageous use of the drug in connection with orthopedic surgery. By its use prior to operative and non-operative procedures it has, by reducing pain, swelling and spasm and by diminishing the activity of the infectious process, not only favorably influenced the result of such procedures but in some instances made possible their use.

The use of the drug subsequent to operation has decreased the likelihood of a post-operative flare-up of the disease and has favored an early and more extensive return of function. Thus better results have been accomplished by the combined treatment than by either method alone.

Ordinarily improvement occurred, if at all, after the first few injections, generally earlier in the more acute cases and more slowly in those of longer standing. In some instances improvement was delayed until the end of the first course and in a few instances no improvement was noticed until some time after the completion of the first or even the second course. In the latter instances the patients, who were discharged at first without evidence of improvement, later returned showing definite beneficial effects of the treatment. In all cases the final improvement as recorded has been maintained at practically the same point to the present time.

A consideration of the improvement gained, based on the age groups, indicates that better results are obtained in the younger patients as was also the case in the first series. Such greater improvement is not due to occurrence of a milder form of arthritis at a younger age since the most severe forms occur in early and middle life. It seems definitely related to such factors as increased general resistance, better general health and in particular better and more adequate function of the circulatory system. Old age itself however constitutes no absolute bar to improvement and of the 10 patients 50 years old or more, five were markedly or moderately improved.

As stated in the first report the degree of permanent or semi-permanent deformity or crippling bears more importantly on the likelihood of improvement than any other single factor, as might be expected. Of the 45 patients with little or none of this type of deformity or crippling, 31 or 68 per cent were markedly improved; of the 32 with marked or moderate deformity 14 or 43 per cent were markedly improved. It is true that in many of the latter cases the deformity was of a mechanical nature which naturally could not be expected to respond to drug therapy and required mechanical (orthopedic) treatment which should of course be employed in these cases in conjunction with the drug. Moreover it should be born in mind that such deformities in themselves tend to favor the persistence of the infectious process and their correction, often times made possible by the preliminary use of the drug, has been of great aid in securing a general improvement in the disease. Reference has already been made to improvement gained by the drug alone in the case of patients thought to have relatively permanent deformities. In such cases one cannot but conclude that the crippling was less permanent and mechanical than had been thought.

The duration of the disease is of importance in regard to improvement only in so far as it is related to the occurrence of the deformities referred to above. Long duration in itself is of no particular significance (if acute cases are excepted) and of the 12 cases in which the disease had lasted ten years or more six or 50 per cent were markedly improved. Most of the cases

of simple (acute) arthritis were greatly improved as might be expected, since many of them improve spontaneously or with a variety of forms of treatment. O-iodoxybenzoic acid however did seem of value in the acute cases by giving more prompt improvement than the usual methods and seemed of particular value in these cases which showed a tendency to become chronic. The gonorrhoeal cases especially, which frequently exhibit this tendency to chronicity, were markedly benefited in most instances.

Considering the various forms of arthritis, the largest group was that of the atrophic (proliferative) variety. This group showed generally more improvement than the group of hypertrophic (degenerative) arthritis. However seven of the 15 cases of the latter type showed marked improvement, a larger number than were expected from the experience of the previous series. Included in this group were a number of cases with extensive involvement of the spine (spondylitis rhizomelica) and the degree of improvement in some of these cases, particularly the disappearance of pain, and increased range of motion, was surprising. In general however such cases offer a less hopeful prognosis than is the case with the atrophic (proliferative) variety. To some extent this is undoubtedly due to the more frequent occurrence of the hypertrophic (degenerative) form in old persons, in whom disturbances in circulation influence adversely the progress of the disease and the results of treatment. Attention has already been called to the occurrence at times of both proliferative and degenerative

changes in the same patient. It seems possible that the presence of atrophic (proliferative) changes, which more readily respond to the drug, may explain the unusual improvement seen in some of the cases classified as hypertrophic arthritis.

Of particular importance is the relation of the degree of improvement to the amount of treatment as shown in Table VI. The association of greater improvement with more treatment is natural and is seen in many diseases but it should also be borne in mind that those patients receiving the greater amount of treatment were in general patients with the more severe forms of the disease. On the whole the patients in the series here reported received more treatment than those of the previous series since the use of eight treatments to a course was more general. It is worth noting that of the 36 patients receiving two or more courses of treatment, and who may, in general, be assumed to have a more severe form of disease, 58 per cent showed marked improvement as contrasted with 60 per cent in the group receiving but one course and who, as a group, were probably less severely affected. Of the three patients who received three or more courses of treatment, and who had a very severe form of the disease, two obtained marked improvement.

A study of the failures is important and valuable in any attempt to determine the value of a given form of treatment. In Table VII is summarized certain data regarding the 12 cases in whom no improvement whatever was obtained. In six cases treatment was inadequate for one reason or an-

TABLE VII.  
TREATMENT WITH O-IODOXYBENZOIC ACID.  
SUMMARY OF DATA IN CASES SHOWING NO  
IMPROVEMENT

	No. of Cases.
1. Treatment Incomplete (Refused 2; Pneumonia 1; Hematuria 1) ..	4
2. No Active Disease (Deformities only) .....	2
3. Failure to Cooperate .....	2
4. No Disease (Malingering) .....	1
5. No Explanation (one course, 1; two courses, 2) .....	3
Total	12

other. In two cases active disease was absent, mechanical deformities alone remaining. In one case it was questionable whether arthritis (sacroiliac) was actually present and malingering was suspected. The remaining three patients simply failed to show improvement without any apparent cause for the failure. The case of the patient who developed hematuria while under treatment is discussed more fully below. In no case was any patient made worse, temporary reaction from the treatments excepted.

#### METHODS OF ADMINISTRATION

As stated above, the patients in this series were given the drug intravenously. Smith in his first paper (2) reported considerable success from its use by mouth and by rectum but later (3) stated that he had found it much more effective given intravenously. Observations by the author are as yet too incomplete to warrant a conclusion as to the value of the drug by mouth. It is undoubtedly effective to some extent and can be given without any particular discomfort but so far it has not appeared to be sufficiently effective to warrant its use by mouth in-

stead of intravenously. From the experience gained thus far it has seemed best to use it intravenously whenever possible and if not to use it per rectum. Rectal administration has the advantage of permitting its use by the patient at home and it is possible that treatment per rectum may be worth while as supplementary treatment between courses of intravenous treatment.

One gram (intravenous) has proven the most effective average dose although larger doses (1.5 grams) may be given in most cases without ill effect and smaller doses may be advisable at times, particularly on starting the treatment and in those specially sensitive to the drug. Bi-weekly treatments are to be recommended since more frequent use tends to cause gastro-intestinal disturbances and less frequent treatments are definitely less effective. No necessity exists for limiting the courses of treatment to eight or ten injections and longer courses may be given if desired. Courses of eight treatments were selected largely on the basis of economic factors and four weeks has proven to be a fairly satisfactory period for active treatment in the average case. Likewise six to eight weeks seems to be a suitable rest period in most instances. Treatment should however be individualized according to the needs of each patient, providing caution against insufficient treatment is observed. Treatment per rectum should, to be effective, be employed over a longer period than in the case of intravenous treatments. It should be emphasized however that references to treatment per rectum should not be construed as a recom-

mendation of that form of treatment over treatment by vein in cases where the latter method can be employed.

#### ACTION OF THE DRUG

No attempt will be made in this paper to discuss the action of the drug except for its bearing in a small way on certain clinical observations. As Smith has pointed out, the drug possesses a salicylate like reaction which is of interest in view of its structural similarity to salicylic acid. However, studies not to be reported here in detail show definitely the absence of any excretion of salicylate in the urine. Although it contains an atom of iodine the absence of iodism associated with the use of the drug suggests a lack of any ordinary iodide effect.

Its resemblance to the salicylates is most noticeable in its analgesic effect although the latter seems more powerful and lasting than is the case with salicylates. However the drug seems to have other and more delayed actions, particularly that associated with improvement in the general health. It seems possible that these effects may be associated with its action on antibody formation described by Hektoen (4) and Arkin (5).

Clinical observations suggest a relation between its action and changes in the circulation, observations which are of particular interest in the light of recent studies on the effect of circulatory changes in joint disease (6). If this be true it is apparent that although it may prove to be effective generally in arthritis associated with pain, swelling and spasm, the extent of its beneficial action may vary in different forms of arthritis according to the

circulatory changes present, as has been observed clinically. On such a basis may be explained its lessened effectiveness in the degenerative forms and in other types of arthritis in old people.

### REACTIONS

No serious reactions were encountered in any of the cases. Nearly all the patients experienced the immediate reaction described in the previous report. Briefly it consisted of burning and stinging in the eyes, nose and throat and at times over the entire body. Most patients described it as similar to the sensations associated with eating mustard or pepper. Lacrimation frequently occurred and occasionally salivation. Flushing, sweating and tingling in the extremities were associated symptoms. Not infrequently patients complained of increased pain in the affected joints which sometimes lasted for twelve to twenty-four hours and was usually interpreted as a favorable sign. Occasionally a sense of suffocation or of pressure in the sternal region was noted. Nausea was rather frequent and occasionally there was vomiting. The latter symptom was very variable and some patients would take nearly a whole course without difficulty only to vomit with the last injection. Others vomited with the first treatment but not subsequently. Both eating and abstinence from food before treatment influenced this symptom favorably in different patients. While vomiting, if it occurred, was usually associated with the immediate reaction it occasionally was delayed an hour or more. In two cases a slight diarrhoea was noted the day following

treatment on one or two occasions. A few patients complained of drowsiness the afternoon of the day following the treatments.

A late reaction, consisting of chill and fever occurring one half to two hours after injection, was noted in many of the acute and some of the chronic cases. In the author's experience this late reaction with chill and fever has been associated with a febrile type of the disease and other signs of an active infection. With improvement such patients became fever free and failed to develop this type of reaction. There is no evidence that improvement or the action of the drug was necessarily dependent on the occurrence of this febrile reaction and improvement without it was common.

The immediate reaction described above was usually over within a few minutes to an hour and most of the patients were able then to resume their usual activities. Some of the ambulatory patients returned to work. Those who reacted more severely were more or less incapacitated for twelve to twenty-four hours but practically all such were comfortable the next day.

In no case in this series were the reactions sufficiently severe to lead us to discontinue treatment and but one such case has occurred in all the patients treated. In the latter case (not included in this series) a rash, of the nature of a toxic erythema, appeared after the first treatment and was accompanied by rather severe nausea, vomiting and diarrhoea. The rash disappeared promptly and a second treatment caused no return but was followed again by a gastro-intestinal dis-

turbance. This and the mental reaction of the patient led to the discontinuance of treatment, a decision influenced partly by the fact that the patient had already received considerable improvement. Only two patients in this series refused further treatment because of the severity of the reactions and in neither instance did the reactions seem, objectively, particularly severe. On the contrary practically every patient has been anxious to continue the treatments, sometimes insisting even when it was felt that no further benefit could be secured. We are consequently at a loss to explain the apparently severe reactions reported to us by some users of the drug although it is probable that some of the reactions encountered during the early use of the drug were due, as suggested by Smith (2), to decomposition products resulting from the use of the free acid. The use of the stable ammonium salt has undoubtedly contributed to reducing the occurrence of severe reactions and Smith in a second communication (3) reported much less severe reactions using the ammonium salt than he had observed with the free acid.

Three patients, not included in this series, but including the case referred to above, developed a skin rash of the nature of a toxic erythema. In two cases it followed the first injection and in the other it occurred after four or five treatments had been given. In all it disappeared in two or three days, and subsequent treatment was not followed by a reappearance of the rash. In no case were the symptoms of iodism observed.

The occurrence of thrombosis of the vein at the site of injection has con-

tinued to be an unpleasant feature. Its frequency has been lessened by the use of the ammonium salt and can be further lessened by careful technique and by washing the drug into the vein with physiologic salt solution. Individual susceptibility to thrombosis as noted in the previous report is an important factor, and the occurrence of thrombosis is also related to the size of the vein and the rate of injection, probably on the basis of physical trauma and dilution factors. The frequent necessity of using small superficial veins in many of the patients, particularly those in the more deforming stages of the disease, tends to make such unfortunate occurrences more common. In no case however has a slough or other severe injury occurred, even when the drug has been accidentally injected outside of the vein wall, and a sore arm for a few hours with a subsequently occluded vein (temporary or permanent) has been the only ill effect observed.

The occurrence of gross and microscopic hematuria during treatment in one case (Table VIII) led to discontinuance of treatment. Such an occurrence would be of particular importance were it thought to be the effect of the drug. However, since such a phenomenon has never been encountered in any other case and since discontinuance of treatment had no effect on the hematuria and there were no other signs of renal injury it was not thought to be the effect of the drug.

No specific contraindications to the use of O-iodoxybenzoic acid have been found but in general it has not been used, nor does its use seem advisable,



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No specific contraindications to the use of O-iodoxybenzoic acid have been found but in general it has not been used, nor does its use seem advisable,

in such conditions as nephritis, heart failure, diabetes, tuberculosis, thyrotoxicosis and the like.

It should be unnecessary to state that in the treatment of arthritis, as in any disease, all measures that benefit the patient should be employed and reliance should not be placed on single measures alone if more than one form of treatment is indicated. Attempts to remove the cause of the disease should be made whenever possible. In the case of the patients in this study further opportunity has been given to observe the need for close cooperation with the orthopedist in the management of these cases. Reference has already been made to the use of curative and prophylactic orthopedic procedures in combination with the use of O-iodoxybenzoic acid. Protective measures in particular are necessary, not only to prevent deformities due to the effects of the disease but to guard weakened joints, muscles, tendons, etc., as these parts again become functionally active. It is to be remembered that such injured structures offer decreased resistance not only to infection but also to mechanical injury from use. Proper footwear, avoidance of occupational strain, restriction of activities to within the limits of tolerance, proper appliances, etc., are all essential for securing the maximum of improvement and particularly that type of improvement which could not be expected to result from the use of the drug alone.

#### SUMMARY AND CONCLUSIONS

Of 80 patients with infectious arthritis treated with O-iodoxybenzoic acid

nearly three fourths were markedly or moderately improved; the remainder showed little or no improvement. No serious untoward effects were noted.

These results substantiate the findings of an earlier report by A. G. Young and the author. Further evidence is given that O-iodoxybenzoic acid is of value in the treatment of infectious arthritis and in the opinion of the writer the results obtained by its use under comparable circumstances, are superior to those obtained with other forms of medical treatment. It is believed that a continued and more extended trial of the drug is warranted in order that its ultimate value be ascertained.

#### NOTE

Since this paper was written Trauba has reported (7) the results in 31 cases of chronic arthritis treated with O-iodoxybenzoic acid. His results, while not as favorable as those previously reported, are encouraging, particularly in view of the type of case treated and the amount of treatment given.

It should be pointed out, however, that because of the variety of modes of administration used his results should not be compared directly with those in which the drug was given almost solely by the intravenous route. Also, treatment in many of Trauba's cases would probably be considered insufficient. Of the 19 cases in which little or no improvement was obtained, treatment was probably incomplete in 15 and of these 11 received less treatment than was advised in the original report by Young and Youmans.

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# The Histopathology of the Tonsil in Acute Rheumatic Fever and Chorea\*

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THAT there is often a close clinical relationship between tonsillitis and acute rheumatic fever is an established fact. With this in mind, many individuals have conducted investigations relative to the bacteriological and pathological aspects of both tonsillitis and rheumatic fever. Inasmuch as the scope of the subject at hand has not embraced a consideration of its bacteriologic phases, our interest in the results of these endeavors has centered around those appertaining to the histopathological pictures obtained in the various tissues of man, and of the experimental animal. In this regard the recent work of Clawson, (1) who has demonstrated in the rabbit that "nodular inflammatory areas showing a cellular reaction similar to that found in human Aschoff bodies are produced in these cases of myocarditis," has been in agreement with the views to those who believe that the streptococcus viridans group is intimately associated with the etiology of acute rheumatic fever. On the other hand, Miller (2) has encountered lesions containing lymphocytes and endothelial leucocytes in sixty per

cent of apparently healthy, adult rabbits used as controls in an experimental study on the transmission of the virus of rheumatic fever.

Since Aschoff (3) described, in 1904, the myocardial lesion which now bears his name, numerous observers, notably Coombs (4, 5), Klotz (6, 7), Swift (8) and Pappenheimer and Von Glahn (9, 10, 11) have identified similar proliferative cellular reactions in the aorta, peripheral arteries, synovial membranes of joints and tendon sheaths, cutaneous and subcutaneous nodules, pericardium, pleura, and probably in the central nervous system. From these observations it is obvious that the distribution of this granulomatous-like lesion is more extensive than was formerly believed. In the light of this knowledge, one is rather surprised to find that relatively few attempts have been made to subject the tonsils to similar microscopic studies. Virtually all who have investigated the tonsils along these lines have failed to find a lesion which could be regarded as characteristic of acute rheumatic fever Dietrich (12), Heiberg (13). In fact, MacCallum (14) has said "at least, no definite and characteristic lesion of the tonsils that would fix their position in relation to rheumatism has been described." Moreover, some

\*Read before the Association of American Physicians, Atlantic City, May 4, 1927. From the departments of Medicine and Otolaryngology, Mercy Hospital.

years ago, one of us (15) was unable to demonstrate in the tonsil any histological picture which could be considered suggestive of rheumatic fever. As a rule those who have studied the tonsil histologically have confined their efforts largely to the tonsillar tissue proper, nor have they attempted to correlate the clinical types of rheumatic fever and the pathological findings in the extirpated tonsils, although Hambrecht and Nuzum (16) found peritonsillitis in one-third of their cases of rheumatic fever.

Stimulated by the knowledge of the wide dissemination of a distinctive lesion of rheumatic fever throughout the human body and the experimental animal; cognizant of the failure to find similar morphological responses in the lymphoid elements of the tonsil; and aware of the well-known association of tonsillitis and rheumatic fever, we undertook to examine, microscopically, the tonsils which had been removed from a series of clear-cut, unquestioned cases of acute rheumatic fever and chorea, and to correlate the clinical data of each case with the pathological processes noted in the tonsils of the same case. Furthermore, we decided to focus our attention on the capsular and periscapsular tissues of the tonsils. This decision was made for three reasons. Firstly, because previous studies by one of us, and by others, had failed to reveal convincingly characteristic lesions in the tonsillar tissue proper; secondly, because alterations in structure, especially cellular proliferative changes can be more satisfactorily observed in these regions; and thirdly, because we had observed at the time of tonsillectomy an

unusual degree of peritonsillar inflammation or fibrosis in the majority of the cases of rheumatic fever and chorea. These tonsils were so adherent by virtue of the extensive inflammatory reaction that the ordinary lines of cleavage were obliterated, so that their removal was accomplished only by deliberate dissection. In those instances of recent acute rheumatic fever, following in the wake of an acute tonsillitis, the gross picture of the pericapsular tissues was that of extreme vascularity, which was out of all proportion to what one might expect from the appearance of the tonsils in situ. When the rheumatic attack antedated the operation by a longer period of time, a uniformly diffuse capsular and pericapsular fibrosis was encountered. The wide-spread distribution of this fibrous tissue was quite different from the patchy or localized deposits so frequently seen in old quinsy beds; nor was it thick and dense as the scar tissue occurring in the inveterate sufferer from peritonsillar abscesses. Whether or not the peritonsillitis was recent or old, the tonsils were always firmly fixed in their fossae.

We wish, therefore, to emphasize three features of this study. One, that all of the cases presented clear, frank manifestations of acute rheumatic fever or chorea; two, that a close correlation between the clinical findings and the pathological pictures was made in each instance; and three, especial attention was directed to the microscopic study of the capsular and pericapsular structures of the tonsils.

Our purpose in presenting this communication is to report the results of eighteen cases of acute rheumatic fever

and five cases of chorea, so studied and so observed.

The tonsils were placed in Zenker's solution immediately after their removal and blocks for microscopical sections were cut so as to include the maximum amount of the pericapsular tissues. In tonsils of a flattened character it was possible to include the capsular and pericapsular areas in one section, but in the rounded forms several sections were often necessary. In addition, one cross section of the tonsil was made in order to study its lymphoid elements. The sections were stained routinely by phloxin-methylene blue, and by hematoxylin and eosin.

Of the eighteen cases of acute rheumatic fever, thirteen were males and five were females. Their ages ranged from 12 to 52 years, five being in the second decade of life, nine in the third, three in the fourth, and one in the sixth. The average age was 26.8 years. In seven instances there was a history of previous attacks of acute rheumatic fever; of these, three had one, three had had two, and one had three previous attacks. Fourteen of the group had suffered from tonsillitis, of whom six had experienced only one attack and in eight, the tonsillitis had been recurrent. Four denied knowledge of tonsillar infection. Those individuals who had only one attack of tonsillitis said that it had occurred immediately, or very shortly, before the onset of the acute rheumatic fever. The tonsils were removed in from two days to six months following the subsidence of the rheumatic symptoms, one-half of the cases coming to operation in from two to four weeks afterwards. We considered this time inter-

val to be safe. In all probability the tonsils could have been enucleated earlier without danger, as Morris (16) has indicated. Ten of the rheumatic cases yielded clinical evidence of valvular heart disease, which was diagnosed as mitral regurgitation in seven, mitral stenosis in two, and aortic regurgitation and mitral stenosis in one. Five individuals showed an albuminuria and one had an acute glomerulonephritis.

Five cases of chorea were similarly studied. Of these four were females, aged four, ten, twelve and fourteen years, respectively; and one was a boy of twelve. The average was 10.4 years. One of the five cases had had a previous attack of chorea and three of them gave a history of tonsillitis, one of whom had suffered from only one attack, whereas in the other two, tonsillitis had been recurrent. The tonsils were enucleated from each member of this group after the manifestations of chorea had subsided but had not disappeared. In general, a comparison of the clinical data with the pathological findings revealed that the more severely acute, and the more prolonged recurrent cases exhibited the most distinctive lesions. However, it is interesting to note that in two cases of recurrent rheumatic fever with mitral stenosis the response to the infection in the peritonsillar regions manifested itself as a very dense fibrous tissue, devoid of any mononuclear elements. One of these, a fatal case, also failed to show Aschoff nodules in the heart, but did present marked perivascular fibrosis of the coronary arterioles.

Microscopically, in the eighteen individuals with rheumatic fever, bone and cartilage, was encountered in two cases and cartilage occurred alone in three, a total of five. Fourteen of the eighteen cases showed varying degrees of perivascular infiltration, usually lymphoid and plasma cell in type. Proliferation of the endothelium of the capillaries and the perivascular lymph spaces occurred in eight cases, in five of which the character and the arrangement of the endothelial leucocytes, with multinucleate forms, suggested the granulomatous lesion described by Aschoff (3). One case showed an acute phlebitis. Bone and cartilage was found in two of the five choreic children, aged twelve and fourteen years, respectively. A lymphocytic and plasma cell infiltration occurred around the peritonsillar blood vessels in four instances. Endothelial proliferation in the capillaries and pericapsular lymph spaces was seen three times, and was shown best in one case with violent chorea, mitral stenosis and albuminuria.

The capsule of the tonsil, a fairly dense fibrous structure, blends with the pericapsular connective tissue so that the two may be regarded as one structure. The pericapsular connective tissue, of somewhat looser appearance, supports muscle bundles, adipose tissue, mucous glands, blood vessels and nerves. It is a very difficult matter to speak with certainty as to the presence of mild grades of fibrosis in this structure. As age advances, the connective tissue becomes denser which must always be considered in speaking of fibrosis in this situation. In about one-half of our cases fibrosis of the

pericapsular tissues was present. In some it was very marked, so much so as to be easily recognizable at the time of the removal of the tonsils. To a certain extent the chronicity of the rheumatic fever appeared to have a direct relation to the more advanced grades of fibrosis. It may be of interest to note that fibrosis of the tonsil, itself, does not necessarily occur with pericapsular fibrosis. Where this fibrosis was marked, dense bands of fibrous tissue were found invading the numerous muscle bundles, causing the muscle fibres to be separated, compressed or often to be completely replaced by the connective tissue. The outstanding feature of the fibrous connective tissue was its collagenous character. Although loose and edematous at times, it was usually dense and compact. Curiously enough, the presence of fibroblasts was rare. We do not regard the fibrosis about the tonsil as an essential lesion of rheumatic fever, but from our material we have noted a relationship between the chronicity of the infection and the subsequent pericapsular fibrosis. Nor was it surprising to find islands of bone and cartilage in the pericapsular tissues in thirty per cent of our cases. True it is that this percentage is not much higher than that given by Weller, (18) although our own figures in a previous study (15) were much lower (3 per cent). There is nothing especially characteristic in the findings of bone and cartilage in such a high percentage in our series. It merely bespeaks a chronic inflammation and it would seem to indicate that the pericapsular tissues in rheumatic fever are involved in chronic inflammatory processes in a higher



proportion than arises from other causes.

Two changes were noted in the muscle bundles in the pericapsular tissues. Normally, the bundles are numerous and their outlines, and striations, are distinct. In some instances they were found compressed, distorted and atrophied by the invasion of the fibrous tissue. Many fibres had entirely disappeared and every gradation of change could be seen. The second alteration in the muscle was an interesting one. Associated with an active cellular infiltration of lymphoid, plasma and endothelial cells, some of the adjacent muscle fibres were split off from the main bundles by an edematous connective tissue. When these muscle cells were atrophic, they were invaded by endothelial leucocytes, forming multinucleated or giant cells. This was noted in two cases. Giant cells of muscle origin are not to be confused with the perivascular multinucleated cells of endothelial origin, to which we shall refer later. Whitman and Eastlake (19) claimed that the large multinucleated cell of the Aschoff nodule in the myocardium was of muscle-fibre origin. Their conception, however, has not been generally accepted and we believe that in the peritonsillar tissues the muscle multinucleated and the endothelial multinucleated cells can be distinguished.

Moderate thickening of the walls of the arterioles was encountered in those cases where considerable fibrosis in the pericapsular region occurred, but we would emphasize the fact that in estimating the degree of this thickening the age of the patient must be consid-

ered. There is no reason why arteriosclerosis cannot involve the tonsillar arterioles in elderly individuals. We did not find any example of excessive thickening of the arterial walls, nor any calcification of them ever seen. Fibrous thickening of the adventitial coats of the arterioles was occasionally encountered. None of the above vascular changes can be attributed solely to rheumatic fever, inasmuch as they may arise in other conditions and particularly in those individuals past middle life.

An acute and chronic phlebitis in a vessel of small size was seen in a case of severe rheumatic fever with a mitral stenosis. In the wall of the vein, the normal structures had been almost entirely replaced by the dense infiltration of lymphoid and plasma cells, and polymorphonuclear leucocytes. There was no thrombus formation, although the lumen contained erythrocytes and many polymorphonuclear leucocytes. An acute lacunar and follicular tonsillitis was present. We do not recall having seen a similar lesion in the pericapsular tissues of the tonsil, although Proskauer (20) described an acute phlebitis associated with peritonsillar abscess. No abscess, however, was found in our case.

In these sections which showed active cellular infiltration, some of the contiguous capillaries presented a well-marked endothelial proliferation. This proliferative change was also found in the lining cells of the perivascular lymph spaces. At times, these cells were large and multinucleated. Moreover, we observed a mitotic figure in a perivascular endothelial cell in a case of chorea. *This endothelial reaction,*

which we encountered in almost one-half of our cases, is a definite one, and we believe, an important one. It is not possible to say that it is specific for rheumatic fever or chorea, although we have not observed this reaction in any other condition.

The mucous glands which lie at the upper pole of the tonsil have an intimate relationship to peritonsillar infection, especially quinsy, as one of us (15) pointed out some years ago. We have frequently noted lymphocytic, plasma and endothelial cell infiltration in the stroma of the mucous glands in cases where the remainder of the capsular tissue was free from inflammatory cell reaction. This observation suggests the possibility that infection may be harbored in the region of the mucous glands. The mucous glands, themselves, often presented changes indicating varying degrees of secretory activity or at other times degeneration. On three occasions there was a diffuse granulomatous reaction in the stroma about the mucous glands. In all of these, the production of large, foreign-body giant cells was a prominent feature. We believe that their formation was secondary to degeneration of the mucous glands.

*Discussion.* Lymphoid and plasma infiltration in the capsular and pericapsular tissues of the tonsil may be caused by a variety of infections of the tonsils, as has been shown by Davis (21) and by Kellert (22). Consequently, the occurrence of this type of infiltration in three-fourths of our cases was not surprising, but it should be remembered that the degree of this infiltration varies greatly, ranging from dense, collar-like, perivascular collec-

tions in some, to isolated cells, diffusely scattered throughout the stroma, in others. At times, there was little or no cellular response, save for an occasional eosinophile or tissue mast cell which occurred, as a rule, in the fibrous tissue.

The most distinctive lesion encountered in this study was a proliferation of the endothelial cells lining the smaller vascular channels and the perivascular lymph spaces. Many of these cells assumed multinucleated forms and on one occasion a mitotic figure was observed in an endothelial cell lying in the perivascular space. This finding was further evidence of endothelial activity. No demonstrable thrombus was associated with this alteration of the endothelium.

Not uncommonly, the endothelial, lymphoid and plasma cells were arranged in granulomatous structures, suggesting the Aschoff nodule. These granulomatous nodules were observed in one fourth of our cases and in none of the control cases.

Our series of control cases has not been large so that we hesitate to place this endothelial reaction, in a category of a specific one for rheumatic fever or chorea. It is to be kept in mind, however, that controls must be very carefully selected in order to obviate the possibility of admitting an unsuspected case of rheumatic fever; as for example, it is well known that a proved mitral stenosis not infrequently occurs in the absence of a history of rheumatic fever or chorea.

#### *Conclusions*

1. In eighteen cases of rheumatic fever and five of chorea a study of the capsular and pericapsular tissues of

the tonsil showed perivascular lesions consisting of lymphoid and plasma cells, in fourteen of the former and four of the latter. In addition to this, atrophic muscle giant cells, fibrosis, bone and cartilage, and foreign-body giant cells in various parts of the tonsil were encountered.

2. An endothelial proliferative reaction of the lining cells of the capillaries and perivascular lymph spaces was noted in eleven cases.

3. Some of the endothelial cells

were multinucleated and were associated with granulomatous-like lesions in six instances.

4. The endothelial cell response was the outstanding feature in this study. We are not prepared at this time to state that it is a specific reaction in the tonsil for rheumatic fever or chorea.

The authors wish to express their gratitude to Dr. S. R. Haythorn for his valuable suggestions and to Dr. H. H. Permar for his aid in the preparations of the material for microscopic study.

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# Uncomplicated Exudative Synovitis

(With Report of Two Cases)

By E. C. ROBICHAUX, M.D., *Excelsior Springs, Missouri*

**Y**OUR attention is invited to the report of two rare types of monoarticular exudative synovitis. Neither was intimately associated with acute or chronic arthritis of whatever kind, nor the immediate result of acute or chronic traumatism. One was definitely intermittent and recurrent in type, the other occurred but the one time. The etiology in both is admittedly obscure.

*Case I.* M. L.; aged 40; weight 220; manufacturer. Admitted October 1926 complaining of swollen knee. He was seen in three separate attacks at long intervals between. Despite the years which separated them, each attack had the main characteristics of the other. Eight years ago, he was suddenly seized with a marked swelling of the left knee entirely incapacitating him during the time of its progression. He noticed a distinct periodicity of occurrence in these attacks which progressed to a climax in two days, and then receded in two days to complete quiescence for nine days. At the end of this time it recurred, observing with each repetition, the same exacting cycle. This had continued for two years when he was first seen. Mineral waters, hydrotherapy, quinine and cacodylate of sodium were used and the condition had vanished in five weeks.

Three years later, without provocation, this condition returned. The onset was sudden. The same knee was involved. The calendar-like precision was observed of four days with and nine days without symptoms.

The knee was very large but not hot. The pain was pronounced only when the joint was brought into use. It had been in progress three months when he presented himself and meanwhile, no treatment had been used. This time *Liquor Potassii Arsenitis* (Fowler's Solution) alone was tried and under its influence there was noticed first, a gradual delay in the appearance of symptoms and later, a diminished intensity until they had vanished altogether in five or six weeks. No other form of medication was used. *Belladonna* was begun but abandoned because of apparent idiosyncrasy.

And now the last attack which occurred also about three years later, coming on as before without apparent physical or psychical irritation. The same knee was once more involved and showed about the same behavior as in the preceding attacks. There were no other symptoms than those found and complained of in the knee.

The family history fails to record any allergic phenomena. The personal history is unimportant except, that, he reports having had many attacks of inflammatory rheumatism and that he denies absolutely any venereal infection. His marriage is without progeny. His temperament, phlegmatic.

*Examination:* Tonsils out and also all devitalized teeth. Sinuses normal. Thyroid normal. The heart measures normal; there is no aortitis. There is no mitral leakage. The blood pressure is 130 over 70. The abdomen is firm and not protruding. The liver and spleen are not palpable; and no symp-

toms elicited from the gall bladder or appendix. The prostate and its adnexae are negative. The Wassermann is negative, as also the urine. Reflexes are normal. R. B. C. 5,000,000; W. B. C. 4,800; Polys. 69%; Hem. 95% (Leitz). Food allergy tests by intracutaneous method, of all foods commonly used are negative. The response to adrenalin is indefinite. Stereoscopic X-ray films in the antero-posterior and both lateral diameters made in 1923 and again in 1926 show no evidence of trophic changes at the margin of the joint surfaces. There is no destruction of articular cartilage, and no evidence of chronic thickening of the periarticular tissues.

*Diagnosis:* Uncomplicated Exudative Serous Synovitis or Intermittent Hydrops.

*Treatment:* Because the patient responded satisfactorily to the use of arsenic in the two previous attacks, neo-arsphenamine suggested itself. An immediate improvement was noticed after the first dose in that the following attack was a mere blush of others before it. There was no further trouble and a total of 5.6 grams at stated intervals completed the work.

*Comment:* It might be said that in intermittent hydrops, everything in medicine and surgery has been tried, including the use of blistering, bandaging, cauterizing, aspirating, injecting of substances like iodine, iodoform, carbolic acid, and finally the open operation. Of drugs, quinine, arsenic and belladonna have been the most popular. It is interesting to note that in this particular case, at least, arsenic in one form or another has

proved of undoubted efficacy. I wish to emphasize the immediate result obtained with the use of arsphenamine.

The rarity of this type of exudative synovitis attracts attention. Only forty-three uncomplicated cases appear in the literature and of these only five were contributed by American authors. Dance (1) in 1831 was the first to recognize this mysterious phenomenon. He called it "Tetanos Intermittent." The report of it was made the year before his death. Perrin (2) in 1845 reports a case of the polyarticular variety occurring at night and reproducing the symptoms every seven days. Omitting all between, we find that the last report in the literature of this condition was made by MacLelland (3) of two cases in 1919.

Men and women are affected about equally. The joint most involved is the knee, although, the hip, shoulder, elbow and wrist have suffered from this peculiar malady, singly or severally. When more than one joint is involved, there is a tendency to maintain a certain regularity of alternation for the given case. In most instances the onset is sudden. The incidence is between the ages of twelve and fifty-four with an average of twenty-six years. A definite cycle is usually established for each case and varies but little during its history. The average duration of each divisional attack is three or four days, and the recurrence may continue indefinitely.

The extremes found are as follows: One case in which the symptoms lasted one hour daily and the case of Benda (4) in which the symptoms lasted eighteen to twenty-one days with an

interval of only eight days before making its appearance all over again.

There may or may not be pain, heat, redness and spasm. Subjectively, languor, headache and chilliness are common symptoms in the attack. The etiology is obscure. Osler (5) believed that it might be a manifestation of hysteria. Some have regarded it as syphilitic, others as allergic, others again as of focal origin. (6) The more popular belief is that it is a vasomotor neurosis.

*Case II.* T. M. C., male, aged 30, admitted March 2, 1926, complaining of severe pain and swelling in the left knee. Ten days before he attended a dinner after which several in the party had a gastro-intestinal upset. Blame was credited to a crab meat salad eaten that night. Four days after he developed a swelling of the knee, attended with much pain and fever. On examination, the knee was semi-flexed, hot and moderately distended with fluid. There was a line of redness, much as one finds in a spreading cellular infection, beginning at the inner aspect of the knee and extending roughly to a point marking the junction of the lower with the middle third of the thigh. The patient was highly neurotic. The fever was irregular, some days intermittent in character, and other days plainly remittent in type. The range of fever was 102 degrees. There was much sweating. Anorexia pronounced. Tongue coated. Heart, liver, spleen, abdomen, normal. Teeth rayed normal and tonsils out. W. B. C. 10,000, 8,000, 7,400, on March 4, 6, 11 respectively; polynuclears 72 to 62. Uric acid 1.1 mgs. to 100 c.c. of blood. Wassermann, negative and also the complement fixation test for Neisserian infection. Prostate negative. The urine contained a trace of albumin and pus, two plus, which cleared up in a few days. The serum drawn from the knee was cultured for thirty-eight hours and was negative, as also the guinea pig inoculation. Blood culture was not made. All

other probable foci of infection were diligently searched for and negatived.

*Treatment:* Complete rest; hot packs, adrenalin in repeated doses at short intervals, salicylate of soda in large doses and iodides were useless. On the twelfth day of admittance and eighteen days after the onset of symptoms, I removed 30 cc. of fluid by needle which gave so much relief that another was done in twelve hours. No more was needed. The patient made a quick and uneventful recovery after that. He has been well ever since.

*Comment:* No similar case could be found in the literature. The probabilities are that this attack had its origin in the intestinal tract. Just how remains a mystery. There is no drinking to account for a possible accident at this time and no other illness of any kind prior to this development.

There is no doubt that some cases of arthritis and synovitis are the outcome of allergic sensitivity but we should then expect the articular disturbance to disappear promptly upon the omission of the offending foods. The clinical findings, plainly of infection, the long duration of symptoms, (in all twenty days) the futility of adrenalin point to some thing else than allergy. The same reasoning might apply to the theory of vasomotor neurosis. Arthritis may develop after an infection of the intestinal tract as Mutch (7) recently demonstrated in his analysis of 200 cases. Any local irritation of the intestinal mucosa might sufficiently interfere with the circulation of the blood or lymph to offer "an opportunity for infective bacteria to establish areas of infection," most often streptococcic, involving great lengths of the intestine, or it might be limited to certain cir-

cumscribed zones of greater activity from which might follow a secondary manifestation such as we have here.

Whatever the cause of this synovitis, it seemed the outcome of a sudden, transitory and aborted type of infection. In fact, the problem had apparently resolved itself very soon into one of distension sufficient to interfere with absorption.

#### SUMMARY

1. A report of two cases of monoarticular exulative synovitis of obscure etiology. One is the so called "Intermittent hydrops" of which only forty-three uncomplicated cases appear in the literature. There were three main

attacks of this mysterious phenomenon in six years and the interesting feature of them is, that each subdivisional attack retained, throughout, its original uncanny calendar-like cycle of progression and retrogression.

2. The efficacy of arsenical preparations is demonstrated by its successful use in each attack.

3. Record is made of the employment of arsphenamine in this case, with almost immediate result.

4. A report of an uncomplicated monoarticular exudative synovitis of undetermined etiology, with the evidence pointing to the gastro-intestinal tract.

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## Editorial

### *THE POSSIBILITIES OF DANGER IN THE USE OF ULTRAVIOLET LAMPS*

If there is any one who reads this editorial whose memory goes back to the seventies of the last century he may recall perhaps some deep impression made upon his young mind by the talk of "blue glass." It was at the height of its vogue about the time of the Centennial, but was a popular fad rather than one countenanced by the regular profession. The latter looked more or less askance at the "blue light" practitioners, who flourished in the larger cities of the eastern states, and carried on thriving business, particularly with a clientele of wealthy neurotic individuals of the sanitarium or watering-place type. "Blue light" clubs were formed, sewing and missionary societies and ladies' literary clubs met in verandahs enclosed with blue glass; many people all over the country introduced panes of blue glass into their houses; and indeed no family was quite up to date if it did not possess a front hall with a fan—and side-lights of blue glass. At a later period these became red. There were many features about this blue glass craze that in the light of our recent knowledge are very interesting, and one book written upon the subject by a Bostonian much earlier in the development of the blue light cult makes entertaining reading. Be-

fore the eighties this fad had almost completely died out, only here and there individuals perpetuated the former belief in some peculiar efficacy of blue light by continuing to put blue panes of glass in their houses. At present the country is rushing into another excess concerning the use of light, ultraviolet rays; this time with a certain foundation of scientific knowledge and fact as a justification. As a result of the recent diffusion of knowledge concerning the important part played by sunlight, and particularly by the ultraviolet end of the sun's rays' spectrum upon all life, there has arisen almost over night a popular demand for artificial sunlight that has met with an all-too-eager commercial response. On every hand we hear people saying that they have purchased ultraviolet lamps and are using them with great benefit to themselves. During the present winter, which has been one unusually free from respiratory infections, it has been a frequent subject for conversation, that "since using our ultraviolet lamp, we have not had a single cold, although in previous winters, we had constant colds." Even physicians swell the chorus and tell tales of happy individual experiences of the same kind. Local electric shops are advertising so-called ultraviolet lamps at six and nine dollars per lamp. Self-treatment then with ultraviolet gen-



erators has in this way been widely spread, and is still spreading rapidly. Such generators promise fair to be as common household articles as the hot-water bag or electric pad. The propaganda for the self use of artificial sunlight is one of very great force, and the arguments irresistible. If sunlight is necessary to human health and happiness, when for several winter months of gloom, chill and depression, the sun is exerting its influence in the southern hemisphere and we are languishing in its absence, if artificial sunlight is possible and obtainable, it surely is folly not to make use of it. There could be no more unanswerable argument. So artificial ultraviolet light is being utilized daily in home, office and elsewhere to help those who can afford its use to get through the winter. Many of the athletic clubs and bathing establishments, particularly those connected with sanatoriums, have seized upon the ultraviolet generator as an important adjunct to their paraphernalia. Nude men and women spend an hour or more daily exposed to light of unknown quality and uncertain power. There is no physician's control of such exposures, and the important thing is that light may be dangerous as well as beneficial and necessary to the normal metabolic processes of the animal body. There is, moreover, such a thing as too much light, as well as too little light. There is such a thing as too much sunlight, as sun-burn, various skin and eye affections, and unpleasant "light reactions" show. Many cases of tuberculosis are definitely harmed by light treatments and exposure of the nude

body to sunlight. The useful and good facts that we do know about the action of light are extremely vital, but it is just as vitally important to know the limits of the favorable action of light and to recognize its dangers. Experimentation has shown that there is a possible optimum of favorable action beyond which it is dangerous to go. Over-exposure to ultraviolet rays reduces the lymphocytes of the blood, and in this way may possibly lower resistance instead of increasing it. Damage to certain tissues or groups of cells may result from over-exposure to ultraviolet rays; the retina, the germ-cells and the melanophores of the skin may be damaged or even destroyed. Ultraviolet light is a dangerous force, and if actinic generators are used exceeding the spectrum of the sun's rays then there are grave possibilities of danger. This danger might in part be averted by laws passed limiting the spectrum of artificial generators to that of the ordinary sun's rays. Even then indiscriminate use and overuse of the sun's rays may not be advisable, and the advice of a good physician should be given whenever the use of artificial generators is contemplated. It must be borne in mind, however, that the average practitioner is as ignorant of the harmful action of light as the average layman. This lack of knowledge is, however, being supplied by literature upon the subject furnished by the American Medical Association. Its Council on Physical Therapy has made the following report, published over a year ago in the *Journal*. Since that time the public exploitation of

ultraviolet generators has tremendously increased, and it is important that both physicians and laymen be again warned as to the possibilities of danger attending the sale of ultraviolet generators directly to the public and their use by the layman without medical advice.

"The Council on Physical Therapy of the American Medical Association, on the basis of the present available evidence, is convinced that the sale of generators of ultraviolet energy to the public for self-treatment is without jurisdiction. The Council bases its condemnation on the sale of such apparatus for this purpose on the following grounds:

"1. The uninformed public could not take the proper precautions in administering treatments and, as a result, severe general burns or grave injury to the eyes might ensue.

"2. Those not familiar with the possibilities of such apparatus would be led to place unwarranted confidence in the therapeutic value of such treatment by the claims that might be made in the literature advertising such generators, and to undertake to treat serious conditions not amenable to such treatment.

"3. The unrestricted possession of such therapeutic means would tend to deprive people of expert diagnosis by encouraging them to make self-diagnosis.

"4. Such practice would encourage the sale of useless and fraudulent lamps which would be advertised as generators of ultraviolet rays, since the public would have no means at its

disposal to determine the quality or quantity of the radiant energy emitted by such lamps.

"For the foregoing reasons, the Council on Physical Therapy considers as detrimental to public welfare the sale or the advertising for sale, directly to the public, of a generator of ultraviolet energy. Under rule 11 of its Official Rules, the Council will declare inadmissible for inclusion in its list of accepted devices for physical therapy apparatus manufactured by a firm whose policy is in this matter detrimental to public welfare."

#### DR. JULIUS BAUER

Dr. Julius Bauer is about 40 years of age, and is Privatdozent in Internal Medicine, University of Vienna, and a physician-in-chief to the Polyclinic located on Mariannengasse. He has a clinic on Endocrinology, which he holds at the Polyclinic on Mondays and Fridays at 5 o'clock. This is exceedingly interesting and instructive and is attended by many Americans. His chief publications are as follows: Lectures on the General Constitution and Inheritance for Students and Physicians. Second edition 1923. With Dr. Conrad Steins in 1926 there appeared a monograph on "Constitutional Pathology as illustrated by Otology." In 1917, his greatest contribution, a large volume on "The Constitutional Disposition to Internal Diseases," appeared; a second edition in 1921. This is a monumental work of 794 pages. In 1927 his latest work on Internal Secretions appeared.

Bauer is a very interesting personality; he visited America in 1925 and lectured in the East, chiefly at Buffalo. He speaks English fluently and is a splendid lecturer. He has an encyclopedic type of mind and is a persistent student. The College of Physicians is very fortunate in having his acceptance. His great contribution is his idea of Constitutional Pathology acting through inheritance, and influencing the endocrine glands, as opposed to the other conception that the en-

docrine glands in the individual are without influence of family or inheritance and only determined by the character of the individual make-up. Dr. Bauer has also made important contributions to the theory of cancer inheritance. His appreciation of the importance of constitutional pathology and the inheritance of disease make him at the present moment one of the leading minds in the medical philosophy of our times.

## Abstracts

*Respiratory Anaphylaxis, Sensitization, Shock, Bronchial Asthma and Death in the Guinea-pig by the Nasal Inhalation of Dry Horse Dander.* By BRET RATNER, HOLMES C. JACKSON and HELEN LEE GRUEHL (American Journal of Diseases of Children, July, 1927).

Some years ago Ratner studied a group of children suffering from bronchial asthma, the cause of which was traced to rabbit hair. In none of these cases was it possible to obtain any hereditary evidence of protein sensitivity; the opinion was therefore expressed that the sensitization had been acquired through the inhalation of dry dust resulting from the rabbit hair present in pillows, clothing, toys and other articles. In order to prove this hypothesis it was felt necessary to produce in an animal a state of protein sensitivity through the direct inhalation of a dry animal emanation, and, further, to reproduce the symptom-complex of bronchial asthma. Sewall had already in 1914-16 shown that animals could be sensitized by nasal instillation of horse serum; and that on further treatment with horse serum, the animals developed symptoms of bronchial asthma. The oral route was found to be ineffective. In 1917, Sewall announced that he had produced all the features of bronchial asthma in the guinea-pig, and that the origin of this asthma is anaphylactic. He believed that this was not a local hypersensitiveness, but is of general nature. The present research carried out by Ratner and associates came to the following conclusions. Horse dander when used in the dry state or in solution, can serve as an anaphylactogen. The authors present a method for the preparation of dry dander, and for the extraction of an anaphylactogen from this substance. Guinea-pigs have been successfully sensitized by the inhalation of dry horse dander. Shock has been induced

by the inhalation of dry horse dander in guinea-pigs previously sensitized by the injection of dander extract, and they have even been killed by it. Guinea-pigs, sensitized by the inhalation of dry horse dander, when again subjected to the inhalation of dry horse dander after a suitable incubation period showed respiratory symptoms of anaphylaxis. The symptoms noted in the last group are not different from those observed in the human being with asthma. Epinephrine alleviates the symptoms in the latter group in the same manner in which epinephrine affects human beings suffering from an attack of asthma. The nasal route can, if conditions are proper, serve as a portal of entry for foreign proteins, in the dry or liquid state, in the same way that a parenteral injection can do so. The authors believe that foreign proteins may enter the circulation from the nasopharynx; this is based on the fact that death occurred after nasal inhalation almost as soon as after an intravenous injection. The swallowing of dry dander in capsules does not sensitize animals. A state of anaphylaxis was produced in the guinea-pig under conditions that would be regarded as natural, i.e., without the introduction of a substance by direct injection, and therefore supports the theory of "acquired" sensitization in the human being. The experimental data in the animal and clinical evidence in the human being are shown to be so closely related as to suggest the point of view that anaphylaxis in the animal and asthma in the human subject are fundamentally the same. This particular type of anaphylaxis in the guinea-pig induced by the inhalation of a dry animal emanation the authors wish to call "respiratory anaphylaxis" as opposed to anaphylaxis induced by parenteral injections. They believe that the hypothesis of Sewall, that the symptoms produced in

guinea-pigs by the intranasal instillation of horse serum have the essential character of bronchial asthma. They agree also with Sewall and Powell, 1916, that the oral administration of dry horse dander does not play any rôle in this particular type of "respiratory anaphylaxis." Whether asthma, in all instances is an acquired disease, or whether it is hereditary, cannot be answered in finality with the evidence at hand. That a certain predisposition is essential, must be accepted both for animals and human beings. What we are mainly concerned with, however, is that, given a predisposition, one can, by governed factors acquire bronchial asthma or "respiratory anaphylaxis." The authors believe that the evidence presented by them in this investigation strongly emphasizes the theory that the problem of idiosyncrasy or allergy in the human subject and that of anaphylaxis in the animal are closely related.

*Note on Urine Preservatives.* By J. J. SHORT and A. PIATETZKY (Journal of Laboratory and Clinical Medicine, August, 1927).

An ideal urine preservative should have the following properties. It should preserve the urine from bacterial decomposition and the development of moulds or other growths for considerable periods of time under average conditions. It should not interfere either positively or negatively with any of the physical, chemical or microscopic tests in ordinary use. It should be readily soluble. It should not interfere to any marked extent with the normal action of the urine. It should be a solid, and its cost should be reasonable. Since 1925 the authors have tried out a large number of preservatives, such as boric acid, borax, toluene, thymol, resorcinol, salicylic acid, sodium benzoate, urofix, nitro-benzene, dinitrobenzene, nitrophenol, and various other aromatic nitro-compounds, benzoic acid, sodium bisulphate, chinosol and hexamethylamine. The last named they found to be the most satisfactory. For the preservation of 30 cc. specimens they use two compressed tablets, one of 100 mg. hexamethylamine and another

such tablet containing 50 mg. each of acetyl-salicylic acid and potassium nitrate, the latter an inert substance used merely for the purpose of facilitating the feeding of the acetyl-salicylic acid into the compressing machine. The tablets are added simultaneously, and go into solution readily. The cost is extremely low as compared to that of the various urine preservatives now on the market.

*The Relation Between Physique and Performance.* By GEORGE J. MOHR and RALPH H. GUNDLACH (Journal of Experimental Psychology, Vol. X, April, 1927).

During recent years there have been numerous studies of the insane centering about the relationship of bodily habitus to mental disturbance. Kretschmer and other investigators have undertaken to show that there is a marked correspondence between the various forms of physical development and mental disturbance. He specifically contends that the pyknic habitus is characteristically associated with manicdepressive psychosis, while the athletic and asthenic types of habitus are clearly associated with the schizophrenic forms of insanity. Not only does a correspondence of physical build and psychic structure hold true in the field of the abnormal, but a similar correspondence may also be determined among normal individuals. Kretschmer's studies led him to believe that at least two temperamental types may be determined among the normal population and that these two types are related in character to the two major types of insanity. While the manic-depressive insanity is typically characterized by a cyclic variation in mood so that the patient may pass from a state of extreme depression to one of maniacal excitation, among the normal there are many individuals who show the same tendency, although the fluctuations remain in much narrower limits. These individuals Kretschmer considers as of the cyclothymic disposition or temperament. In contrast is that large group who evince in minor degree the characteristics that under pathological conditions become the symptoms of

the schizophrenic disorders. The well-developed symptoms of schizophrenia, such as emotional blunting, disorders of attention and disturbances in the associative processes, may find their correlatives in diffidence, pre-occupation and self-centeredness of certain normal individuals. According to Kretschmer, these are of the schizothymic temperament. Kretschmer further holds that the correspondence of certain types of physique associated with these temperaments, noted among insane patients, may also be demonstrated among the normal. He describes the asthenic, athletic and dysplastic bodily forms. The asthenic individual, said to be of the schizothymic temperament, is one who is of average height but is relatively tall for his weight. He is thin with a long narrow shallow chest. His shoulders are relatively broad contrasted with the diameter of his chest. His muscles are thin and poorly developed. The skin is thin and loosely attached to the underlying tissues. The face is characteristically long and narrow, with a prominent nose and clear-cut features. The facial angle is sharp and the mid-face is relatively long. The athletic type is similar to the asthenic in general bodily proportions, but all of the structures are thicker, firmer and of more robust development. The shoulders are heavy, the chest is broad and of medium depth. The skeleton is heavily built. The muscles are thick and closely adherent. The face is relatively long and narrow, with proportions similar to the asthenic, but with thick though well-defined features. The skin is thick and closely adherent. The face is relatively long and narrow, with proportions similar to the asthenic, but with thick though well-defined features. The facial angle is less marked than in the asthenic and the lower jaw more heavily developed. The athletic type is considered a variant of the asthenic, and is associated with the schizothymic group. The pyknic habitus is described as one in which there is an increase in the volume of all of the body cavities. The head is large, the chest is voluminous and exceptionally broad and deep. Although the shoulders are of moderate width they appear narrow in contrast

with the broad chest. The abdomen is full. The skeletal structure is slight when compared with the general bulk of the individual, and the extremities are relatively small and slender. The hands are small and delicate. There is a generous adiposity, and the skin is thick and firm. The face is round and ruddy and the mid-face is short. This bodily form is associated with the cyclothymic disposition. The dysplastic type includes many deviants from the normal. In this group are those physical forms giving evidence of endocrinal disturbance, such as the eunuchoid, hypoplastic, acromegaloid, adipogenital, etc., forms. In addition to these form-types there are mixtures of the various types, and certain forms that fail to fit into the classification. As to the occurrence of these types in the insane, Kretschmer found, on the basis of study of 260 cases, that 70.3 per cent of the schizophrenic patients present physical forms corresponding with the asthenic and athletic types, and that only 2.9 per cent of these present a pyknic habitus. Of the manic-depressive patients 84.7 per cent presented pyknic build and only 10.6 per cent the athletic-asthenic form. From these findings, together with observations on normal individuals, and from characterologic studies of families of normal psychotic subjects, Kretschmer develops his entire theory of temperament and the association of temperament with physical build. Many investigators have endeavored to determine whether the physical types can be readily identified, and further, to clarify the possible relationship of these physical forms to the insanities. Apparently, there has been little difficulty in the identification of the actual types, but there has been a wide divergence among the investigators as to the incidence of these types among the insane. There is a general agreement that there is a greater incidence of the pyknic build in the manic-depressive group, but there are also reports of typical cases of manic-depressive insanity not associated with the pyknic habitus. Mohr and Gundlach made a study of 89 native white men taken from a large prison population. Of these men 18 were of the asthenic type, 26

of the athletic type and 44 of the pyknic type, conforming to the distinguishing characters and physical measurements for Kretschmer's types. Their conclusions were as follows. The incidence of the physical types among the prison group is not markedly different from that observed by a number of investigators among the schizophrenic patients and that by Gruble among normal individuals. It is similar to that observed by von Rohden among convicts, although the incidence of pyknic forms among the Joliet group is somewhat larger. It is possible that only the lower grades of pyknic men are represented in the convicts. The physical types as Kretschmer describes them cannot be precisely differentiated by mere inspection. There is a continuous progression from the characteristics of the extreme asthenic and those that determine the "best" pyknic habitus. Grouping of the asthenic and athletic men under a single leptosome does not seem to be justified. Whatever the exact significance of the physical types may be, there is no doubt that the differences of performance of these groups can be demonstrated. Tests of "attention" and "learning" show the asthenic groups lower than the athletic subjects in three of the four tests and lower than the pyknic in the fourth. Tests based upon "inhibition" or "blocking" did not distinguish the groups. The characteristics of the cyclothymic temperament, in speed of performance, showed that in

straight reaction time, speed of writing and cancellation the pyknic subjects were decidedly lower than the other groups, while the asthenic group was quite superior. The Raschach test tends to characterize the pyknic men as of a melancholic or manic disposition, while the sociological material indicates a more social life. The results support in a general way the Kretschmer theory of physical and temperamental types, in that a relationship between physique and character of performance is demonstrated. They tend to modify the theory, however, by insisting on the concept of a general progression both of performance and of physical characteristics. The asthenic subjects showed relatively more schizothymic tendencies, the pyknic subjects more cyclothymic tendencies. This bears out the evidence in the literature. The deviations in personality that constitute the symptoms of the insanities and that determine the temperaments may be conceived as ranging from extreme schizoid characteristics on the one hand to extreme manic-depressive characteristics on the other, in a manner similar to the distributions found for both performance and physical measurements. The exceptions are so numerous as seriously to impair the validity of an easily recognizable constellation of physical and psychological attributes as a type. An interpretation of the facts at hand does not require the retention of the concept of "type."

## Reviews

*Modern Medicine. Its Theory and Practice.* In Original Contributions by American and Foreign Authors. Edited by SIR WILLIAM OSLER, BART., M.D., F.R.S. Third Edition, Thoroughly Revised. Re-edited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia, Fellow of the Royal College of Physicians, London; Formerly Associate Professor of Medicine, The Johns Hopkins University. Assisted by Elmer H. Funk, Assistant Professor of Medicine, Jefferson Medical College, Philadelphia. Volume V. Diseases of the Blood—Diseases of the Lymphatic System—Diseases of the Ductless Glands—Diseases of the Urinary System—Vasomotor and Trophic Disorders—Diseases of the Locomotor System. 948 pages, 82 illustrations. Lea and Febiger, Philadelphia, 1927. Price in cloth, \$9.00.

The contributors to this volume include Thomas Brown, Richard Cabot, George Dock, Charles P. Emerson, Sir A. E. Garrod, Harold W. Jones, Edmund B. Krumbhaar, H. Lissner, W. T. Longcope, John McCrae, Thomas McCrae, Archibald Malloch, J. P. O'Hare, Sir William Osler, J. H. Pratt, L. G. Rowntree, W. R. Steiner, A. S. Warthin and H. H. Young. Chapters I and II on The General Pathology of the Blood-forming Organs and Pernicious and Secondary Anemia, Chlorosis and Leukemia are by R. C. Cabot. These articles have not been brought up to date, particularly the two on pernicious anemia and leukemia. The author does not seem aware of much new thought concerning these diseases. The importance of the constitutional factor in pernicious anemia as emphasized by Faber and many others is not mentioned; the discussion of the etiology is inadequate, and there surely should have been time to in-

corporate into the proof-sheets a fuller discussion of the dietetic treatment of this disease. As this article stands its paragraphs on treatment are practically useless to the practitioner who will consult this new volume for recent information concerning pernicious anemia. Likewise, the section on Polycythemia is not up to date. The relationship of polycythemia to diseases of the pulmonary arteries is not considered. Ayerza's disease is not even mentioned. Pratt's articles on Purpura and Hemophilia are brought up to date and are very complete and well written. Krumbhaar's section on Diseases of the Spleen is also written with a knowledge of the recent literature, and is adequate. The same thing may be said of Jones' chapter of Blood Transfusion. Chapter VI, on Diseases of the Lymphatic Glands has been brought up to date. A typographical error on page 222 reads reticulocytosma for reticulocytoma. In Chapter VII Longcope presents the infective granuloma view of Hodgkin's disease without commitment to any known etiology. His entire article is written from this standpoint, and he is apparently unfamiliar with the transitional forms between aleukemic and leukemic lymphocytomas and Hodgkin's, and the "reticulocytomas" or "reticulocytosarcomas." George Dock and H. Lissner have written the chapters on the Ductless Glands, Adrenals, Pituitary Body, Pineal Gland, Thyroid and Parathyroids. These articles are complete and well brought up to date. The same may be said of the chapter on Diseases of the Thymus by Warthin. The various divisions of Part IV, Diseases of the Urinary System have been largely revised by Roundtree, Thomas McCrae, James P. O'Hare, Thomas R. Brown and Hugh Young. The first three have attempted the difficult task of revamping the older knowl-



edge of the non-purulent forms of kidney disease from the standpoint of the modern terminology of the nephroses and the nephritides and to harmonize the clinical and pathological discrepancies. This attempt is not always quite successful, but the articles are conservative and at the same time progressive, and free of the old dogmatism of clinical and gross pathological classification, and are, therefore, very valuable treatments of this complicated subject. The more properly surgical affections of the kidneys are adequately treated from the medical standpoint. Part V, Vasomotor and Trophic Disorders, originally written by Sir William Osler, has been revised by Archibald Malloch, and presents a very complete discussion of these conditions. Part VI, Diseases of the Locomotor System, Myositis, Myotonia Congenita, Myotonia Atrophica, Amyotonia Congenita, are given very adequate treatment by Walter R. Steiner. Arthritis Deformans is discussed by Thomas McCrae; Osteomalacia by Dock, and other diseases involving the skeleton are treated by C. P. Emerson. With the exception of a few instances the revision of this volume has been complete, and the majority of subjects treated are well brought up to the moment and are valuable discussions well suited to the practitioner's needs.

*A Textbook of Pharmacology.* By A. D. BUSH, B.S., M.D., Professor of Pharmacology, Emory University, Georgia. 182 pages. P. Blakiston's Son and Co., Philadelphia, 1927. Price in cloth, \$2.00.

The author says in his preface that this book on Pharmacology is written to meet the needs of the student of pharmacy and the practicing physician, since they are so busy that they cannot afford time to waste in the sifting search for essentials to which they must subject the usual textbook on Pharmacology. When a practitioner perceives the need for a medicine, he wishes to know quickly just how and where that medicine will act, what symptoms the medicine itself will produce, what symptoms it will allay and just what is the preferred method of utilizing the medicine for this

particular purpose. Answers to these questions are given systematically and concisely in this book. The book is divided into three parts:—Part I, Pharmacology; II, New and Non-official Remedies; III, Prescription Writing. The general scheme is to give the name of the drug, average dose, official preparations, source, leading utility in medicine, where and how its effects are produced, usage for obtaining effect, symptoms produced by drug, symptoms it allays, leading side actions, related utilities in medicine, elimination, toxicology and contraindications. It is another handbook designed as a short and easy cut to the use of drugs in medicine, and has consequently all of the defects of the short manual. The author claims that though the student of pharmacology may later read more extensively elsewhere, he will learn elsewhere little more that is of essential value, and will return again and again to this text with the comforting assurance that here indeed is a Pharmacology that furnishes for him the very things he wishes to know. If this is true modern courses in Pharmacology in our University Medical Schools need to be revised.

*Outlines of Pathology In Its Historical, Philosophical and Scientific Foundations.* A Guide for Students and Practitioners of Medicine. By HORST OERTEL, Strathcona Professor of Pathology, McGill University, Montreal, Canada. 479 pages, 132 illustrations including 6 colored plates. Renouf Publishing Co., Montreal, 1927. Price in cloth, \$10.00.

The publisher heads his advertisement of this book with "A New View of Pathology." The author in his foreword says that "it will be apparent at once to those familiar with the subject that the scope and manner of the presentation differ in some important respects from those generally followed in textbooks. It is based on the method of teaching pathology at McGill, which deals with it primarily, not as a practical medical or premedical subject, but as a scientific and cultural branch of knowledge, and endeavors to up it in its proper setting. For this purpose the stu-

dent is introduced to it, not by taking him through its present structure, and in direct application to the art of healing, but from the standpoint of historical, philosophical and scientific orientation. In other words, he is taken to the threshold of the subject and prepared to enter it himself. To this end an effort is made to unfold critically the origin of, and trace the different methods of attack upon, the great problems in pathology, and to emphasize its constant interactions with other sciences and the theory of knowledge." The author calls his book a guide not a textbook. Another quotation is to this effect—"It seems to me much more important to open the windows of the student's mind and obtain his interest and cooperation than to burden him with nauseating thoroughness of details which change from day to day." It is evident at once that the author has a complex of pessimism directed against the modern textbook which he deplores as having been written under the influence of publishers looking for large sales, and resembling a show window in a Woolworth shop more than anything else in the world. He is determined apparently that his book should not be called practical. He believes that his book should present pathology as a science which has nothing to do with humanitarian or teleological aspects, or the relief of human ills, but solely with the determination of the lawful order and explanation of diseased life. He believes that it is much more important for the undergraduate student to obtain a clear, intelligent understanding of the general conceptions of disease, than to spend time on some one's insecure classification of streptococci, or to memorize the details of the test methods of liver function, or the various modifications in the operation for inguinal hernia, or the dosages of over a hundred pharmaceutical preparations. The first is a cultural, permanent acquisition, with which the university is principally concerned; the second are technical details of which the student himself must become master by his own, and not the instructor's volition. It is the principal purpose of the university to cultivate and refine the judg-

ment of the students in order to fit them for an intelligent pursuit of their career. In this respect there is no distinction between "theoretical" and "practical" training for even practical application in professional careers can be based on intelligent reading. Oertel believes that pathology is at present less in need of individual efforts in discoveries and new findings than of a strictly scientific critical method. He sympathizes with the practitioner of medicine today, "drowned in a scientific mess which he is unable critically to sift." These quotations and excerpts from his Foreword are perhaps sufficient to show that this textbook on pathology is conceived in the nature of a protest against the handbook or manual type of textbook of pathology of which we have had so many published in the United States, and which present to the student only categories and catalogues of supposed scientific facts (which may be changed next year) without any unity of philosophical conception or treatment. With such a view and protest the reviewer is wholly in sympathy. Three things are necessary for a successful textbook; it should hold the known and accepted scientific knowledge of the subject; these should be held together by the fundamental philosophy of the science; and the future development of the science should be indicated whenever new lines of experimental investigation open up new paths of thought. Only when all three of these are fully taken account of can the resultant textbook be really practical and cultural. The interlarding of medical history, poetical and classical quotations, and the like, does not make of pathology a cultural course. These matters and other pertinent digressions are for the class room and the teacher, not for the textbook. The latter should be the foundation stone of the science it represents, the cultural presentation of this knowledge depends upon the teacher, his culture and his personality. While agreeing most heartily with Oertel's main thesis that pathology should be taught for its cultural value as well as for its practical (medical or hospital) application, the reviewer is convinced that this cultural value

depends upon the teacher and not upon the textbook. Classes differ, students differ, and each year's teaching, or mode of approach, must vary. Cultural teaching is a thing of the spirit, and cannot be reproduced in the black and white of a textbook; but the latter must serve as the solid foundation of fact and theory upon which the cultural should be developed by the teacher and in the student's mind itself. Culture can be given as milk or water, in overdoses, just as much as the mess of theory and facts of which Oertel so bitterly complains, but from which incubus he cannot wholly free himself. He acknowledges at the close of his foreword that "for didactic reasons" he has not entirely broken with the past, but followed it in form and contents as far as he considers compatible with this standpoint. How successful is his treatment? His contents are divided into three chapters: Chapter I, the Conception of Disease; II, Etiology and III, Pathogenesis. An epicrisis follows. The material is presented in a narrative style, at times conversational. At times this method has the advantage of catching the reader's

interest, at other times a certain vagueness or looseness is produced which will leave the student in as much of a mist as the categorical presentation of facts would ever produce. Some parts are extremely good, notably the paragraphs on heredity, somatic development, parasitism and immunity. Other sections appear very incomplete, particularly the general discussion of neoplasms, the specific infections and inflammation. Disturbances of development are very inadequately treated. The protective forces of the body seem also to be incompletely considered. Etiology, except for parasitism, is too cursorily treated. The chief criticism of this book is, therefore, that of inadequacy. Nevertheless, it has great individual value. It is more refreshing and stimulating in its contrast to the average manual type of English textbook on pathology. Inadequate, when compared with the great textbooks of pathology, Aschoff and Tendeloo, this book should be recommended for collateral reading to all medical students who read in English only. We warmly advise its use for this purpose.

## College News Notes

Dr. Oscar B. Hunter, F.A.C.P., of Washington, D. C., was recently elected the head of the District Medical Society there. Dr. Hunter is Professor of Bacteriology and Pathology in the George Washington University Medical School, Consulting Pathologist to the Casualty Hospital, the Montgomery County Hospital, and the Sibley Memorial Hospital, and has been active in local and national medical societies.

FOUND—Fellowship Key. Mr. John H. Dwyer, of Dwyer Bros. Lighterage, No. 4 Coenties Slip, New York, New York, has reported that on January 17, 1928, he found a watch fob with a Fellowship Key attached, on a Staten Island Ferry Boat, South Ferry, New York City. The owner can secure same by communicating with Mr. Dwyer.

"By ruling of the U. S. Commissioner of Internal Revenue, The American College of Physicians has been approved for exemption from income tax, and all amounts (Initiation Fees, Life Membership Fees and Dues) contributed to The College shall be deductible from the gross income of such donors when filing Income Tax Returns."

### PAYMENT 1928 MEMBERSHIP DUES

The Executive Offices mailed to every Associate and Fellow of The College, a statement for 1928 dues on January first. A large percentage have already taken care of this obligation, and Membership Cards have been mailed to them. Others are urged to mail their checks promptly to the Executive Offices, in order that Membership Cards may be issued for admission to the New Orleans Clinical Session, and for

entry on the subscription list to ANNALS OF INTERNAL MEDICINE.

### OBITUARIES

Dr. Thomas H. Grosvenor, Wenatchee, Washington (Associate, April 3, 1922). Died December 11, 1927, of cerebral hemorrhage; aged 54; M.D., Northwestern University Medical School, Chicago, 1908; staff, St. Anthony's Hospital; ex-president, Chelan County Medical Society; member, Northwest Medical Society, Washington State Medical Society and Fellow of the American Medical Association.

Dr. William Henry Foreman, Indianapolis, Indiana (Associate, February 24, 1926). Aged 60 years; M.D., Central College of Physicians and Surgeons, Indianapolis, 1902; Associate Professor of Medicine, Indiana University School of Medicine.

James Campbell Todd, Boulder, Colorado (Fellow, December 30, 1921). Died January 6, 1928, following a long illness; age 53; Ph., B. Wooster College; M.D. University of Pennsylvania, School of Medicine, 1900; Postgraduate study at Harvard University Medical School; Assistant Lecturer, Associate Professor and Professor of Pathology, Denver and Gross College of Medicine, Denver, 1904-10; Professor of Pathology, University of Colorado, School of Medicine, 1910-15; Professor of Clinical Pathology, University of Colorado, School of Medicine, 1915-00; Member of Phi Gamma Delta, Phi Alpha Sigma, Phi Beta Kappa, and Sigma Xi Fraternities; Author of "Clinical Diagnosis by Laboratory Methods;" Member of local, county and state medical associations and of the American Society of Clinical Pathologists.

Meeting of  
THE AMERICAN COLLEGE OF  
PHYSICIANS

NEW ORLEANS, MARCH 5-9, 1928

PROGRAM

Corrected and Brought Up to Present Date

MORNING SESSION, MONDAY, 10:00

Address of Welcome, Mayor Arthur O'Keefe.

Address of Welcome, President A. B. Dinwiddie, Tulane University.

Address of Welcome, Dr. J. Birney Guthrie, President, Orleans Parish Medical Society.

Address of Welcome, Dr. C. C. Bass, Dean, Tulane University School of Medicine.

1. Dr. Julius Bauer, Vienna, Austria, "Adaptation and Compensation as Origin of Disorders."

2. Dr. David P. Barr, "Multiple Myeloma."

3. Dr. L. G. Rowntree and Dr. George E. Brown, "Studies in Blood Volume with the Dye Method."

4. Dr. Joseph Sailer, "Cardiac Conditions Contraindicating the Use of Digitalis."

5. Dr. Frank R. Menne, "The Effect of Iodin on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

EVENING SESSION, MONDAY, 7:45

1. Dr. Maud Sly, "Cancer and Heredity."

2. Dr. Aristides Agramonte, Havana, "Review of Research in Yellow Fever."

MORNING SESSION, TUESDAY, 10:00

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."

2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."

3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."

4. Dr. C. C. Sturgis, "The Treatment of Pernicious Anemia with a Liver Fraction."

Symposium on Tuberculosis.

5. Dr. Charles L. Minor, "Modern Trends in the Treatment of Tuberculosis."

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

EVENING SESSION, TUESDAY—7:45

1. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

2. Dr. James S. McLester, "The Influence of Latent Syphilis, So-called, upon the Course of Other Diseases."

MORNING SESSION, WEDNESDAY—10:00

1. Dr. Walter M. Simpson, "Tularemia: A Clinical and Pathological Study of Fifteen Non-Fatal Cases and One Rapidly Fatal Case with Autopsy."

2. Dr. L. F. Bishop, "The Practice of Cardiology."

3. Dr. Morris H. Kahn, "Heart Strain and Its Consequences."

4. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

Symposium on Epilepsy.

5. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

6. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

7. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

EVENING SESSION, WEDNESDAY—7:45

Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."

4. Dr. J. C. Small, "Rheumatic Fever."  
MORNING SESSION, THURSDAY—10:00

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."

2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."

3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the the View Point of an Internist."

Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."

5. Dr. Frederick M. Allen, "Present Results and Outlook of Diabetic Treatment."

6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."

7. Dr. W. H. Olmsted, "The Dietetic Management of the Diabetic in the Doctor's Office."

MORNING SESSION, FRIDAY—10:00

1. Dr. J. L. Goforth, "Natural and Acquired Body Resistance to Neoplasia."

2. Dr. T. Z. Cason, "The Progress of Medical Research in the South."

Symposium on Tropical Medicine.

3. Colonel Roger Brooke, "The Influence of the Tropics on Rickets."

4. Dr. Aldo Castellani, "Metadysentery, with Remarks on the Classification of Intestinal Bacteria."

5. Dr. Wm. M. James, "The Early Lesions of Intestinal Amebiasis."

6. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.

7. Dr. Aristides Agramonte, "Considerations upon the Etiologic Agent of Yellow Fever."

EVENING SESSION, FRIDAY—7:45

1. Dr. Julius Bauer, Vienna. Convocation Address—"Multiplicity of Factors in the Etiology of Disease."

NEW ORLEANS CLINICS.—For information as to the Clinics to be held in

New Orleans, see December Annals, News Notes.

"Following the appearance of Dr. Julius Bauer, of Vienna, Austria, on the program of the Twelfth Annual Clinical Session of The College at New Orleans, March 5-9, Dr. Bauer will be available to appear before medical organizations in various parts of the United States. Dr. John H. Musser, Chairman of the Clinical Session at New Orleans (address, 1551 Canal Street, New Orleans) is arranging Dr. Bauer's itinerary, which will probably include San Diego, Los Angeles, San Francisco, Seattle, Portland, Minneapolis, Chicago, Cleveland, Philadelphia, Baltimore, and New York."

## NEW ORLEANS

The City of New Orleans occupies a unique position among the large cities of the United States, because, besides being over two hundred (200) years old, one of the oldest social, medical and literary centers, the Metropolis of the South, progressive and up to date, it still retains, due to the French and Spanish influence resulting for nearly one hundred (100) years of occupancy, that subtle charm found in the cities of Southern France and Spain. This charm is felt by all those who make it their home, and during your only brief stay amongst us you will see many material evidences of it in the *Vieux Carré* (Old French Town).

But let me tell you about New Orleans, past and present in the words of some of the distinguished writers who have visited it, not only because their word pictures are better than mine could ever be, but in order to spare the modesty of a native son.

In the latter 1840's, Oakey Hall who later became Mayor of New York, speaking of the first St. Charles Hotel, which was completed early in 1837, and since destroyed by fire, exclaimed, "set the St. Charles in St. Petersburg and you would think it a Palace; in Boston (ten to one) you would christen it a College; in London and it would marvellously remind you of an Exchange; in New Orleans it is all three." Lady Wortley, an English woman who had trotted about the globe, and who wrote her

"Impressions of America," has left on record her verdict that the St. Charles was the finest piece of architecture she had seen in any place, in any part of the world. It must be remembered that this was before the United States became the hotel building, and the hotel dwelling country that it later became. In that time there was no Commodore, no Blackstone, nor even a Palmer House, or Pacific Hotel.

The following article, written by an anonymous author in Harper's Weekly of Sept. 3rd, 1859, furnishes an excellent pen-picture of the Charity Hospital, built in 1832, after the earlier hospitals, the first of these erected in 1737, had been destroyed by fire.

The New Orleans Charity Hospital is one of the most celebrated institutions of its kind in the United States. Not only so, but in the liberality of its support, the commodiousness of its buildings, the systematic excellency of its therapeutic arrangements, the number of its beneficiaries, the superior skill of its attending physicians, the admirable neatness of its domestic appliances, and the impartial catholicity of its administration, it will compare favorably with the older and more renowned establishments of England and the Continent.

"Nor is it amiss to say that, whether regard be had to the ability of the Professors or the admirable advantages offered to the pupil, there is no better place in the country than New Orleans for young men who are studying to enter the medical profession."

Frederick Lewis in the October, 1927, number of the Woman's Home Companion, in an article on New Orleans says, "Amongst other things New Orleans possesses many such romantic figures of the near and distant past around whose names have gathered the anecdotes and legends which constitute the peculiar charm of the city's history. Many of them have likewise left their marks on the stones and mortar of the city's present-day structures; especially in the *Vieux Carré*, the old French quarter, where the balconied buildings which line the narrow streets recall the grandeur of other times. Here is the New Orleans that we read about in the

guidebooks and the railway folders; the New Orleans which styles itself "The Paris of America"—the city of restaurants and cafés.

When it comes to New Orleans cooking I could write a book (and eat a library!). But I shall content myself with saying what I have said so many times before—in print and in person to the lovers of good food: Go to Antoine's in the French quarter. Make no resistance when the waiter brings you a tin of villainous looking baked oysters. They are a specialty of the house and remarkably good.

Go to La Louisiane. Order pompano, papillote or bouillabaisse. Go to Galatoire's. Go to a dozen other little restaurants in the back street of *Vieux Carré*. You can't get a bad meal. You may find waiting for you in the unlikeliest of places the choicest banquet of your epicurean life. Or go to Begue's where you begin to eat at eleven in the morning and keep on eating until three in the afternoon.

I can imagine that regular attendance at Begue's might prove fatal. But there are worse deaths. And New Orleans remains interesting—even in matters of interment! The places where the famous figures of New Orleans history lived during their brief period on earth are no more picturesque than the places where their ashes have lain during their long rest in the city's famous cemeteries. The old St. Louis Cemetery, where the unique practice of burying above ground was first instituted, is now closed except for the occasional admission of some long-lived and almost forgotten figure out of the city's past; but the larger and even more picturesque Mairie Cemetery is still the most ornately picturesque of New Orleans' burial grounds.

New Orleans is not behind the times. But she is content to add a few modern improvements; she isn't willing to substitute them for ancient charms. She builds beside, but not on her early glories. She still retains the brightest jewels of her crown."

So come to New Orleans for the Meeting of the American College of Physicians, you are assured a warm welcome, a splendid scientific program, and if the weather is

true to form, a mean temperature of fifty degrees, lots of sunshine and all the vegetation of spring-time.

### POPULAR INTEREST IN THE CARIBBEAN CRUISE

Widespread interest has been aroused among members of The College in the post-clinical session Caribbean Cruise from New Orleans on March 10th. The United Fruit Company has advised that a considerable number of reservations have already been made, and it is anticipated that the capacity of the ship will be taken up by our members. Those who have not yet made reservations but are interested in the cruise, should complete their arrangements at once. For full description of this cruise see December Annals, College News Notes.

### HOTEL ACCOMMODATIONS

#### *New Orleans Clinical Session*

The headquarters hotel for the Twelfth Annual Clinical Session at New Orleans, Roosevelt Hotel, reports that their supply of single rooms for the Clinical Session is practically exhausted from the large number of applications for reservations. There are still available double rooms at this hotel. It should be noted, however, that other hotels listed below offer excellent accommodations and are recommended to our members by the local New Orleans Committee on Hotels and Transportation. The Committee reports that many of these hotels are actually closer to the hospitals offering the clinics than is the headquarters hotel, the Roosevelt.

### LIST OF HOTELS

(All Prices are for Rates per Day,  
European Plan)

- Roosevelt Hotel*, 123 Baronne St. (Capacity 750)  
Single room with bath....\$5.00 to \$ 7.00  
Double room with bath.... 8.00 " 12.00
- St. Charles Hotel*, 211 St. Charles St. (Capacity 496)  
Single room with bath....\$3.00 to \$ 6.00  
Double room with bath.... 5.00 " 8.00
- Jung Hotel*, 1500 Canal St. (Capacity 325)  
Single room with bath....\$3.50 to \$ 4.00  
Double room with bath.... 5.00 " 6.00
- Hotel Monteleon*, 214 Royal St. (Capacity 600)  
Single room with bath....\$3.00 to \$ 4.00  
Double room with bath.... 3.00 " 6.00
- Hotel DeSoto*, 420 Baronne St. (Capacity 400)  
Single room with bath....\$4.00 to \$ 5.00  
Double room with bath.... 6.00 " 8.00
- Bienville Hotel*, Lee Circle, Capacity 300)  
Single room with bath....\$4.00 to \$ 6.00  
Double room with bath.... 7.00 " 10.00
- Lafayette Hotel*, 628 St. Charles St. (Capacity 100)  
Single room with bath....\$3.00 to \$ 3.50  
Double room with bath.... 4.00 " 6.00
- La Salle Hotel*, 1113 Canal St. (Capacity 100)  
Single room with bath....\$3.00 to \$ 3.50  
Double room with bath.... 4.00 " 5.00
- Hotel Louisiane*, 725 Iberville St. (Capacity 38)  
Single room with bath....\$2.00 to \$ 3.00  
Double room with bath.... 3.00 " 4.00



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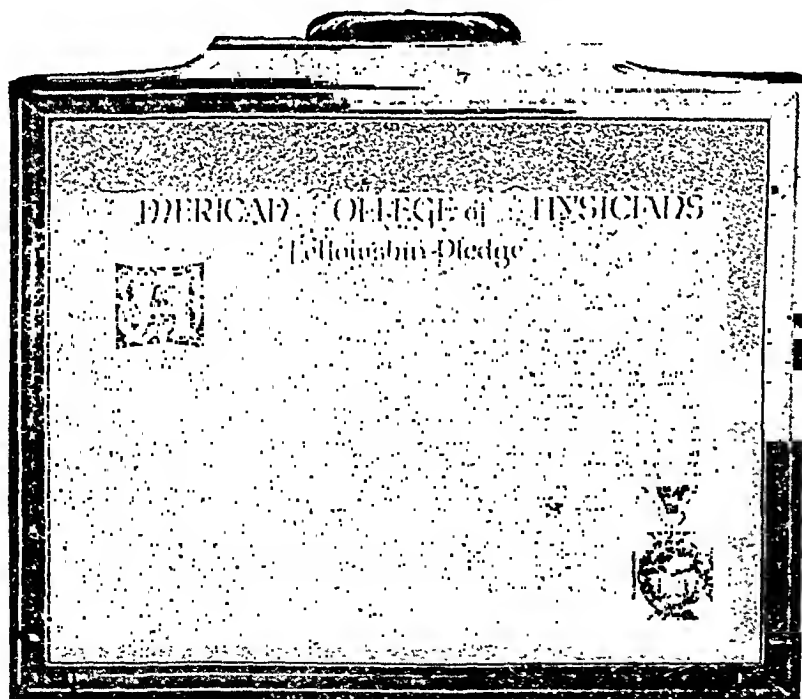
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# Thrombo-Angiitis Obliterans: A Clinical Study of 200 Cases\*

## I. Etiology, Pathology, Symptoms, Diagnosis

EDGAR V. ALLEN, M.D., *Fellow in Medicine, The Mayo Foundation, and*

GEORGE E. BROWN, M.D., *Division of Medicine, Mayo Clinic,  
Rochester, Minnesota*

**S**PONTANEOUS gangrene of the feet in middle-aged patients without arteriosclerosis has been known for many years. In 1879 Winiwarter reported the case of a man, aged fifty-seven, who had complained of rheumatic pains in the feet for twelve years. The pathologic changes were intimal proliferation, thrombosis and periarterial fibrosis; arteriosclerosis was absent. He designated the condition as a peculiar type of endarteritis and endophlebitis. Weiss, in 1895, and Manteuffel, in 1897, reported similar cases from which they concluded that the thrombosis was due to intimal changes of an arteriosclerotic nature. In 1879 Borchard reported five cases and favored the view of Winiwarter. Bunge, in 1901, supported the theory of Weiss and Manteuffel, but his cases seem to have been true examples of arteriosclerotic disease in older patients. In 1908 Buerger reported the results of his study of dissected vessels of eleven limbs amputated from middle-aged Hebrews with spontaneous gangrene in which he concluded that the dis-

ease was primarily an acute inflammation of the arteries resulting in a cellular type of thrombosis. In the older lesions, organization, canalization, and periarterial fibrosis were observed. Because of the inflammatory thrombotic nature of the disease he called it thrombo-angiitis obliterans, which term has been generally adopted. His subsequent publication of larger groups of cases have further substantiated these observations. Todyo, in 1912, correlated the work of former investigators and described diffuse vascular inflammation with intimal proliferation and thrombosis of the lumina of the arteries and veins. In the last ten years many cases have been reported in American and foreign literature.

Two hundred cases of thrombo-angiitis obliterans seen and carefully studied at the Mayo Clinic from 1922 to 1926 inclusive, form the basis of this report.\*

\*Submitted for publication January 24, 1928.

\*Three hundred cases will be reported in detail in the form of a monograph at a later date.

## CLINICAL COURSE

Thrombo-angiitis obliterans, Buerger's disease, or the endarteritis obliterans of Winiwarter, is an obliterative disease of the arteries and veins of the extremities, occurring principally between the ages of twenty-five

which is in turn followed by or associated with marked rubor when the extremities are dependent and excessive pallor when they are elevated. Trophic changes occur either in a minor form, such as excessive callosities in the weight-bearing areas, or

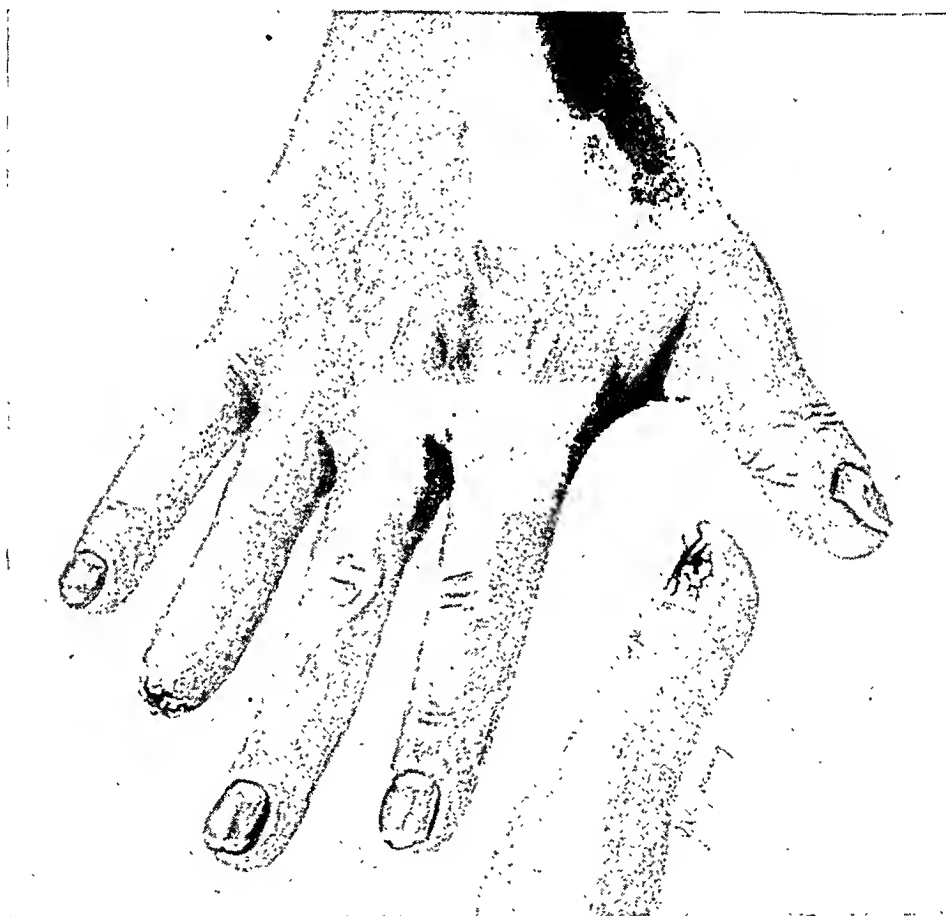


FIG. 1. Thrombo-angiitis obliterans of the hands with an unhealed amputation wound of the fourth right digit and a small ulcer on the left thumb.

and forty-five years, and affecting only males, in our experience predominantly Jews, who are excessive smokers of tobacco. The disease first manifests itself by excessive fatigue in the extremities followed shortly by the pain of claudication (brought on by exercise and relieved by rest)

in the major form as gangrenous ulcers of the digits or gangrene involving the toes or the entire foot (figs. 1 and 2). Before trophic changes occur, pain is usually absent or mild when the patient is at rest; with the onset of trophic changes rest-pain frequently becomes so se-

vere that patients beg for amputation. When the disease is well established the extremities are objectively cold and there is a reddish cyanotic color

ties frequently occurs during the course of the disease and is presumptive evidence of occlusion of the larger veins.



FIG. 2. Thrombo-angiitis obliterans of the right foot with gangrene of the great toe and superficial phlebitis.

of varying degree when they are in the dependent position, and pulsation in the arteries of the feet and legs or upper extremities is diminished or absent. In about 40 per cent of the cases superficial phlebitis is associated at some time during the course of the disease. Edema of the lower extremi-

#### ETIOLOGY

The etiology of thrombo-angiitis obliterans is unknown. It is Buerger's opinion that the disease is of specific infectious or toxic origin, producing its effect primarily in the walls of the arteries and veins. Rabinowitz iso-

lated an organism from the blood in cases of thrombo-angiitis obliterans with which he produced vascular lesions in rabbits somewhat similar to those observed in man. He described this organism as a gram-negative, aërobic, facultative anaërobic, freely motile bacillus of medium size, beaded, bi-polar in appearance and containing metachromatic granules. Rose now and Nickel have cultured the veins resected in acute phlebitis with negative results. Meyer (22) believes that the disease is due to excessive tobacco smoking alone and that the vascular changes are secondary to "saturation" with tobacco smoke. Changed viscosity of the blood is thought to be a factor by Koga and Koyano. Goodman and Bernstein thought latent typhus fever was a factor. Steel believed that the coagulation time of the blood was shortened. Ochsner believed that a high-salt diet was a factor, and Chlumsky thought the superficial phlebitis and the cutaneous nodosities were due to fly bites. That syphilis is not a factor has been demonstrated by Perla, Buerger and Kaliski, and by our studies. In our series, increased viscosity or shortened coagulation time of the blood, diet, typhus fever or fly bites did not seem responsible.

#### POSSIBLE CONTRIBUTORY ETIOLOGIC FACTORS

*Race.*—Although thrombo-angiitis obliterans occurs predominantly in Russian Jews, it has been reported in Swedes by Ochsner; in Chinese by Meleney and Miller, and Whyte; in Japanese by Koyano, and Ito; in

Koreans by Ludlow; in Turks by Wieting; and a questionable case has been reported in a negro by Gemmill. In approximately 50 per cent of our cases the patients were Jews, the remainder beings Austrians, Finns, Norwegians, Germans, Scotch, Irish, French, English, Dutch, Greeks, native Americans, and those of mixed ancestry. Although this disease occurs in almost every known race it has a definite predilection for Jews.

*Smoking.*—Only three patients of this series were total abstainers from tobacco smoking. In a control series of other diseases of cases in which the age was comparable and the sex the same, there were forty patients who did not smoke and the remainder used tobacco less extensively than most of the patients with thrombo-angiitis obliterans. Care must be used in evaluating the tobacco factor as occasionally tobacco smoking is initiated (and usually it is accentuated) after the disease has progressed to the point of causing pain, insomnia and nervousness. However, with full consideration of these factors it is evident that tobacco smoking is much more common in patients with thrombo-angiitis obliterans and may constitute a contributory etiologic factor.

*Birthplace.*—Eighty-six per cent of the Jews and twenty-four per cent of the Gentiles of this series were foreign born. In the control series of other diseases, 75 per cent of the Jews and 28 per cent of the Gentiles were foreign born. This would indicate that birthplace plays no rôle in thrombo-angiitis obliterans.

*Sex.*—The occurrence of thrombo-angiitis obliterans exclusively in men has been noted by all authors except Koyano, Meleney and Miller, each of whom report a case occurring in a woman. Buerger reported three cases in women. Pathologic proof was lacking in the cases of Koyano and Buerger. Meleney and Miller found that the dissected vessels were microscopically similar to those observed in thrombo-angiitis obliterans. All patients of our series were males.

*Syphilis.*—In only 6 (3 per cent) of the cases was the Wassermann test positive. We believe this was due to associated syphilis.

*Foci of infection.*—In eighty-seven cases of this group the teeth were examined roentgenographically, in 75 per cent of these periapical infection was definite enough to be considered clinically important. In 80 per cent of all the cases the tonsils were enlarged and contained plugs or fluid pus. In forty-six cases the prostate was examined by the method of Von Lackum; in 52 per cent prostatitis was marked enough to be considered of clinical importance. In only three cases of the entire group were there no demonstrable foci of infection. The fact that this disease in our experience occurs exclusively in men leads to the impression that the prostate may serve as an important focus of infection but the theory lacks proof as does the impression that any distant foci of infection are of etiologic significance.

*Thermal conditions.* — The first symptoms were noted in cold weather

in 71 per cent of our cases. It is not known whether cold is an etiologic factor or whether the symptoms are first noticed in cold weather because of increased demand for greater circulation. Cold probably plays a contributory or exciting part.

*Occupation.*—Eighty per cent of the patients in this series were active workers, such as farmers, blacksmiths, truck-drivers, brakemen, oil workers, foundry workers, boiler-makers, miners, lumber-yard employees, clerks, electricians, pedlers, carpenters, plumbers, engineers, teachers, shoe-makers, barbers, junk-dealers, bakers and sausage-makers. A control group of an equal number of patients with diseases other than thrombo-angiitis obliterans showed the same percentage actively employed. Occupation therefore has no bearing on the cause of the disease.

*Age.*—All authors have agreed that the limits of incidence lie almost constantly between the ages of twenty-five and fifty. Frauenthal reported a case of bilateral spontaneous gangrene of the hands in a male child, aged three years, which he thought was thrombo-angiitis obliterans, but the data were insufficient for diagnosis. Koyano reported the case of a patient whose symptoms began at the age of nine years. The youngest patient in the present group was seventeen, the oldest sixty-four. In the latter case gangrene and arterial obliteration were present, the history was suggestive of superficial phlebitis, and arteriosclerosis was not demonstrable roentgenographically. The diagnosis was not proved pathologically. The

age grouping in this series was as follows: from fifteen to twenty-five years, six cases; from twenty-five to thirty years, eighteen cases; from thirty to thirty-five years, thirty-one cases; from thirty-five to forty years, thirty-three cases; from forty to forty-five years, thirty-one cases; from

fuse acute inflammation affecting the walls of the arteries and veins, with secondary thromboses. The thrombus is composed of erythrocytes, leukocytes, and fibrin. Purulent foci are formed in the periphery in which giant-cells are observed. With subsidence of the acute reaction, fibro-

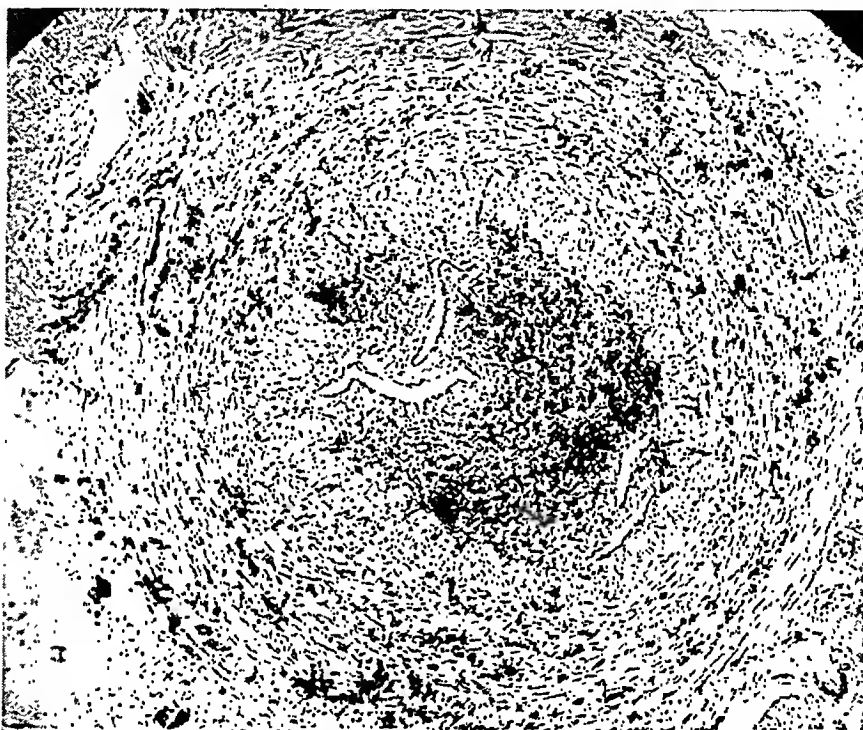


FIG. 3. An artery from a case of thrombo-angiitis obliterans. The lumen is occluded by an organized thrombus which is partly canalized. There is cellular infiltration of the arterial wall and the thrombus.

forty-five to fifty years, thirty-one cases; from fifty to fifty-five years, fourteen cases; from fifty-five to sixty years, three cases; from sixty to sixty-five years, two cases. In the cases in the seventh decade and in some of the sixth decade the diagnosis was not proved pathologically.

#### PATHOLOGY

The earliest pathologic change according to Buerger (7, 8, 9) is a dif-

ferentiation of the thrombus and organization takes place (fig. 3). Angioblasts penetrate into the thrombus forming new vascular channels. Eventually the perivascular tissues, the artery and the vein become included in dense fibrous tissue (fig. 4). The capillary channels coalesce and fairly large vessels are formed in the organized thrombus. Elastic tissue and muscle layers are observed in the

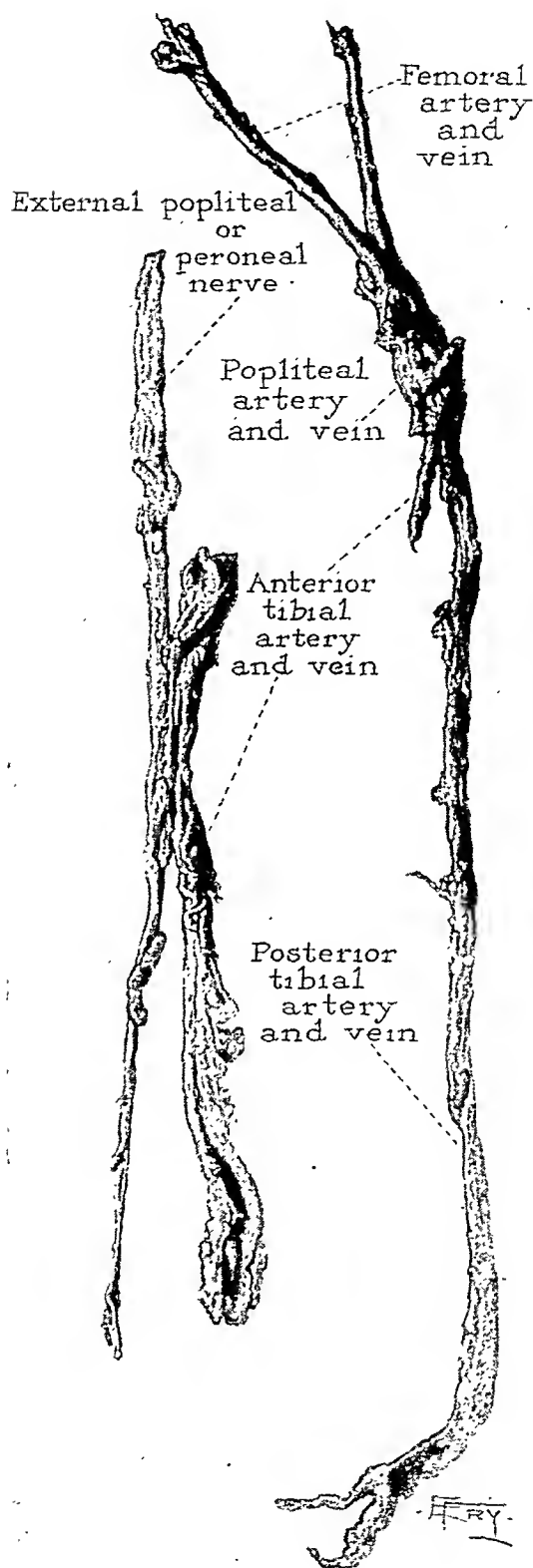


FIG. 4. Vessels dissected from the leg in a case of thrombo-angiitis obliterans showing the perivascular binding.



walls of the older vascular channels. The evolution of the process can be followed by histologic study of the excised segments of the veins involved in the superficial phlebitis. We have studied thirty amputated limbs and eight resected veins pathologically. Mahorner has studied this same material pathologically to determine if possible the prethrombotic changes in the intima. His observations agree essentially with those of Buerger except in respect to the interpretation of the intimal changes; in his experience evidence of acute inflammation was extremely rare. Mahorner found active intimal proliferation in the arteries and veins which was more marked than is found in control subjects of similar age. He describes projections of the intima with deposition of fibrin and platelets on the summits. There was no thrombosis either distally or proximally to the localized intimitis. The chief difficulty in deciding this point rests on the rarity of specimens at this stage of the disease. Changes in the intima would be anticipated on a priori grounds to account for the deposition of the thrombus, as changes in the blood and circulatory disturbances have not been demonstrated in this disease.

#### CLINICAL TYPES

The following forms of the disease were commonly observed: (1) acute fulminating, (2) slowly progressive, (3) nonprogressive, and (4) compensated or healed. Unusual forms of the disease were: (1) extensive gangrene without pain (1), (2) venous involvement only, (3) normally pulsating ar-

teries (3), (4) vasomotor disturbances suggesting Raynaud's disease (2) (5) associated arteriosclerosis, (6) absence of trophic changes, (7) severe rest-pain without trophic changes, (8) absence of symptoms, (9) onset with sudden vascular occlusion, and (10) onset with edema.

#### EARLY SYMPTOMS

Pain of claudication was the first symptom in 51 per cent of the cases in this series. The longest history was fifteen years and the shortest two months. Coldness of the extremities was the first symptom in 12 per cent; the longest duration was four years, the shortest eleven months. Abnormal fatigue was the first symptom in 11 per cent; the longest duration was five years, the shortest four months. Nonhealing ulcer was the first symptom in 10 per cent, the longest duration was six years, the shortest was eight months. Sudden arterial occlusion provoked the first symptom in 7 per cent. Recurrent superficial phlebitis was the earliest symptom in 4 per cent, being of sixteen years' duration in one case. Edema was the first symptom in 3 per cent, and vasomotor disturbances of spastic type only, in 2 per cent.

#### DIFFERENTIAL DIAGNOSIS

We are of the opinion that in no branch of medicine does more confusion exist in the differential diagnosis than in that of the localized vascular diseases. This is mostly because the primary distinction is not drawn between the organic or occlusive diseases and the vasomotor or functional disturb-

ances since color changes (pallor, cyanosis and rubor) may be common to both groups and since they are frequently so striking that they largely overshadow the basic occlusive disturbance. For purposes of orientation, a simple classification of the usual arterial diseases has been proposed by Brown (1, 6). This is not offered as a complete classification but one which according to our experience covers approximately 95 per cent of the clinical types (Table 1). The main division is that between the organic or occlusive and the functional or vasomotor diseases, each of which has a local and a general distribution. Only those of a local distribution will be considered here. We have not included in the classification the syphilitic forms of vascular disease, nor the pathologic rarity, periarteritis nodosa. The organic and vasomotor types can be differentiated in 90 per cent of the cases by determining the state of the pulsations in the palpable arteries of the extremities (Table 2). In 10 per cent of the cases of peripheral vascular disease three particularly confusing types of cases are found: (1) those in which occlusive lesions involve only the distal arteries of the fingers and toes and pulsation in the usual palpable vessels is normal, (2) cases of organic disease with associated vasomotor disturbances simulating Raynaud's disease, and (3) cases of associated arteriosclerotic disease and thrombo-angiitis obliterans.

Two diseases, thrombo-angiitis obliterans and arteriosclerotic disease, make up 95 per cent of the occlusive arterial diseases of localized distribu-

tion. They have, in common, arterial obliteration with symptoms of arterial insufficiency (excessive fatigue or the pain of claudication) coldness of the extremities, excessive rubor with dependence and excessive pallor with elevation. The first occurs predominantly in Jews who smoke heavily, in our experience always men, usually between the ages of twenty-five and forty-five, and in about 30 per cent of the cases associated at some time with superficial phlebitis. The rubor of the feet is intense, minor trophic changes are extremely painful and there is usually a moist, inflammatory reaction around them. The arteries cannot be demonstrated roentgenographically. Arteriosclerotic disease occurs in older persons usually between fifty-five and eighty-five and there is evidence of arteriosclerosis in the extremities and elsewhere. There is no racial preference, women are occasionally affected, there is no associated superficial phlebitis, the rubor is usually milder, the ulcers are less painful and usually dry, and there is no inflammatory reaction. Arteriosclerosis can be demonstrated roentgenographically in most cases.

The early diagnosis of thrombo-angiitis obliterans is most essential. This is relatively simple if one considers the underlying basis of the initial symptoms and the impaired supply of blood. Excessive fatigue, if of relatively short duration in the arch, ankle, or calf of the leg, or of the wrist or forearm, should lead to inspection of the arteries of the extremities. Frequently this important symptom and the pain of claudication, both expressions of anoxemia, are

overlooked and the patient is treated for fallen arches, rheumatism or metatarsalgia, or fitted with special shoes which fail to give relief. When the rubor occurs in the digits, deep-seated infection is occasionally diagnosed in spite of the local absence of heat, and toe nails and finger nails are removed or incisions made. In 50 per cent of our cases of gangrene this had been done, and the gangrene thus initiated. When major trophic changes are present, the diagnosis is usually "gangrene." Frequently no attempt is made to determine the cause, as a result of which toes are amputated, healing does not occur and successively higher amputations are necessary.

The vasomotor or functional form of vascular disease of localized nature comprises two types: the vasospastic and vasodilator. These have in common pulsating arteries in the involved extremities, absence of symptoms of arterial insufficiency and lack of marked changes in color with change of posture. The disturbances are intermittent, and in the early stages complete recovery occurs. These data usually serve to differentiate them from the occlusive lesions (thromboangiitis obliterans and arteriosclerotic disease). The vasospastic type includes a large group of conditions variously designated as acrocyanosis and acroasphyxia; when distinct color reactions are present with pain or trophic disturbances of bilateral distribution the condition is correctly designated Raynaud's disease. The fundamental disturbance is similar in all these conditions, consisting of an hyperirritable vasoconstrictor mechanism in the acral areas. The patients

conform closely to a constitutional type designated by Müller as "vaso-neurotic constitution." Intermittent vasoconstriction of the superficial arterioles, capillaries and veins produces pallor and cessation of the flow of blood in these vessels with depression of superficial temperature. This is followed by dilatation of the skin capillaries with partial resumption of the flow of blood in the capillary loops sufficient to produce dilatation and opening up of the many capillaries but not sufficiently rapid to prevent cyanosis of the capillary blood. The stage of rubor represents a recovery reaction with dilatation of the arterioles and rapid capillary flow with dilated and many open loops; the surface temperature increases.

The vasodilator disorders are characterized by intermittent attacks of burning and redness in the extremities. The feet are hot, the veins dilated, the arteries exhibit excessive pulsations and gangrene does not occur. Many border-line cases are observed. Symptomatic erythromelalgia, that is, burning of the feet without objective evidence of increased surface heat, is frequently associated with arteriosclerosis.

#### SITE OF LESIONS

Koyano in 125 cases found associated involvement of upper and lower extremities in 30 per cent. In four cases in our series reported by Constant, the symptoms were primarily in the hands, due to obliteration of the radial or ulnar arteries or both. In 60 per cent of the forty cases in our series in which the upper extremities were carefully examined there was

complete or partial closure of the ulnar or radial arteries.

There was no noticeable difference in the frequency of involvement in the right and left extremities. The frequency of involvement of the arteries was as follows: the dorsal's pedis, posterior tibial, popliteal, and femoral in the lower extremities, and the ulnar and radial in the upper extremities.

#### LABORATORY DATA

The number of erythrocytes and leukocytes was normal in this group, except in a few cases in which there was marked inflammation around the gangrenous ulcer, usually associated with mild leukocytosis and anemia. The blood sugar and blood urea values were normal. The viscosity of the blood and the platelet count were normal in the few cases so studied. The urine frequently contained a slight amount of albumin, pus, or casts, but these were not considered significant. The phenolsulphonephthalein test for renal function showed nothing abnormal. The cholesterol in the blood by the Bloor I and Bloor II methods in nine cases were at the lower limit of normal and the lecithin and fatty acid were normal in the same cases. Oral temperature and pulse rate were nor-

mal except in a few cases of gangrene or secondary infection in which both were slightly increased. The arteries of the extremities could be demonstrated roentgenographically in two cases of this group indicating associated calcification of the media characteristic of arteriosclerotic disease.

#### SUMMARY

Two hundred cases of thrombo-angiitis obliterans in men have been carefully studied. The pathologic studies were carried out in thirty amputated limbs and eight resected veins, the observations were essentially those described by Buerger except in two regards. The evidence of acute inflammation was extremely rare. Proliferation of the intima was found which seemed out of proportion to the age of the patient. It is felt that these intimal changes may be prethrombotic. Thrombo-angiitis obliterans is apparently a disease of infectious origin. Bacteriologic investigations were made on veins which were clinically acute or subacute but no specific organisms were demonstrated. The diagnosis is relatively simple if the nature of the localized vascular diseases of the extremities is adequately understood.

TABLE I  
TENTATIVE CLINICAL CLASSIFICATION OF ARTERIAL DISEASES\*

Functional or vaso- motor types	1. Multiple-phase color reaction: Raynaud's disease	
	Vasocon- stricting types	Vasodi- lating types
General distri- bution		Primary erythromelalgia
		Primary or essential hypertension (early stages)
Local distri- bution		Primary or essential hypotension
Organic types	2. One-phase color reaction; acrocyanosis, dead finger, local syncope	
	Vasocon- stricting types	Vasodi- lating types
General distri- bution		1. Arteriosclerosis, with or without thrombosis; diabetic gangrene
		2. Thrombo-angitis obliterans
Local distri- bution		3. Arteritis of known infectious origin (rheumatic) (†)
		4. Aneurysm with or without thrombosis
	Arteriosclerosis	
	1. Primary	
	2. Secondary to hypertension	

\*In our experience, this classification will cover practically all the usual forms of arterial disease.

†A pathologic rather than a clinical entity.

TABLE 2  
DIFFERENTIAL DIAGNOSIS OF VASCULAR DISEASE AFFECTING THE EXTREMITIES

	Thrombo-angiitis obliterans	Arteriosclerotic disease	Raynaud's disease and similar conditions	Primary erythromelalgia
Pulsation of peripheral arteries	Absent 50 per cent Diminished 45 per cent Normal 5 per cent	Absent 50 per cent Diminished 45 per cent Normal 5 per cent	Normal	Normal
Excessive rubor with dependence	Present	Present	Absent	Absent
Excessive pallor with elevation	Present	Present	Absent	Absent
Claudication	Usually present	Usually present	Absent	Absent
Gangrene	Common	Common	Rare	Never
Rest-pain	Usually very severe	Usually mild	Usually absent	Usually mild
Type of rest-pain	Sharp, stinging	Aching	Absent	Burning
Appearance of gangrenous ulcers	Moist, inflamed, discharging		Small punched-out areas	None
Superficial phlebitis	30 per cent of cases	Absent	Absent	Absent
Age at onset of symptoms	Mostly between twenty-five and forty-five years	Mostly between fifty-five and eighty-five years	Mostly between seventeen and thirty-five years	Mostly between thirty and fifty years
Sex	Males 99 per cent	Males 90 per cent	Females 95 per cent	Females 70 per cent
Race	Hebrews 50 per cent	Any	Any	Any
Röntgenographic appearance of arteries	Usually no sclerosis	Usually sclerosis	Normal	Normal
Color changes following exposure to cold	30 per cent	15 to 20 per cent	Always	Never
Temperature of extremities	Low	Low	Low	High
Edema	Frequent	Infrequent	Absent	Absent

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# Thrombo-Angiitis Obliterans: A Clinical Study of 200 Cases\*

## II. Treatment and Prognosis

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MANY methods of treating thrombo - angiitis obliterans have been suggested. Chief among these from a medical standpoint is the method of administering sodium chloride solution subcutaneously (Koga) and by stomach tube (McArthur) in order to reduce a supposed increase in the viscosity of the blood; the method of Sinkowitz and Gottlieb for the utilization of the hyperemic method of Bier; the use of diathermy (Wright); the use of white light (Frauenthal); injection of insulin (Ambard, Boyer and Schmid); the intravenous injection of sodium citrate (Steel); and the irradiation of spinal areas (Philips and Tunick). From a surgical standpoint, other than amputation, anastomosis of the femoral artery and vein was carried out by Lilienthal and advocated by Wieting and Meyer. Buerger believed there was a certain type of case in which this was of value, but Oppenheim did not have good results and Stetten col-

lected 136 cases in which the procedure had been attended by a mortality rate of 30 per cent, absolute failure in 72 per cent, and good results in only 11 per cent. Lewis and Reichert reported one case in which benefit followed ligation of the femoral artery. Ginsberg ligated the femoral vein in four cases with slight improvement in one. Silbert injected the nerve in the malleolar region with absolute alcohol; pain was satisfactorily relieved and there were no untoward results. Herzberg analyzed 110 cases of adrenalectomy, fifty-four of which had been observed from six months to two years. The disease was quiescent in eleven, and ameliorated in nine; amputation had been performed in thirty-two. Brown and Rowntree reported the results of periarterial neurectomy, as devised by Leriche, in seventeen cases; they did not find sufficient benefit to justify continuance of the procedure.

There has been an increasing tendency toward conservatism in surgery and prolongation of medical treat-

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ment. This has been justified by a number of facts which have become apparent: (1) pain can be relieved in many cases for a long time by medical measures; (2) in many cases sufficient circulation will be re-established to keep the extremity functionally adequate provided rest or trophic types of pain when present can be relieved; (3) there are many indications that the disease is of a recurrent infectious type, hence attention must be directed to the elimination of foci of infection; (4) with adequate medical treatment amputation can be carried out at a low level in selected cases; (5) lumbar ganglionectomy and ramisection is of value in selected cases, and (6) major trophic changes, such as gangrenous ulcers, are occasionally amenable to medical measures.

*Selection of treatment.*—The type of lesion must be considered in the treatment; five types can be differentiated:

1. Extensive gangrene with or without pain; the treatment is amputation.

2. Mild trophic changes with severe rest-pain; the treatment consists of medical measures for the relief of pain, methods to increase the circulation, prophylactic measures and removal of foci, lumbar ganglionectomy and ramisection may be carried out in suitable cases. If medical measures for the relief of pain are unsuccessful, amputation is indicated or lumbar ganglionectomy and ramisection may be performed in suitable cases.

3. Mild trophic changes without rest-pain; the treatment consists of prophylactic measures, removal of foci of infection, measures to increase the circulation and lumbar ganglionectomy and ramisection in suitable cases.

4. Severe rest-pain without trophic changes; the treatment is the same as that in the second type.

5. Neither rest-pain nor trophic changes; the treatment consists of prophylactic measures, removal of foci of infection and measures to increase circulation.

The economic factor is worthy of more than cursory consideration in the selection of the type of treatment. Palliative or expectant treatment is frequently uncertain in its results and always a financial burden on patients of slender means. This is well illustrated in the case of a Greek waiter with a ten-year history of thrombo-angiitis obliterans. When the first symptoms began he owned a small restaurant, had money in the bank and was well enough situated to be assured of financial independence. With the first symptoms came disability, idleness in hospital and physicians' fees. The principal in the bank was exhausted, the restaurant mortgaged and later sold and the patient became a waiter, unable to work more than two or three days a week, nor to earn more than a precarious livelihood. In ten years he had spent \$10,000 for medical care alone and had spent three years in hospitals. How much better would it have been had amputation been performed when the first symptom appeared! In cases of trophic change or severe pain medical

treatment should not be given unless the patient fully understands the uncertain results and the financial burden involved.

*Medical treatment.*—Medical treatment should include prophylaxis, measures to increase the local circulation, removal of foci of infection and relief of pain. The extremity should be closely protected from trauma and cold. Care should be used in the treatment of minor abrasions as these may initiate gangrene. Calluses should not be incised nor toe nails trimmed too closely. Woolen socks with felt boots are the best protection from cold. Patients should be instructed to rest the extremities as frequently as their occupation allows. Certain types of occupation must be forbidden. If the patients are of adequate financial means, a period of six months to one year of almost complete rest is of great value. Smoking should be interdicted or sharply diminished.

Routine measures to increase the blood supply of the extremity include the so-called contrast baths, that is, immersing the extremity to the knee for one minute in cold water (from 50 to 60°F.) and quickly changing to warm water (from 102 to 105°F.) for the same length of time. This is repeated fifteen times, at least twice daily ending with the warm bath. Radiant heat from the carbon-filament lamp is applied for increasing periods of time. Great care should be exercised to prevent burning. Postural exercises consist in elevating the feet for one minute, hanging them over the edge of the bed for one minute,

and keeping them horizontal for one minute; this is repeated ten times on three occasions daily. Nonspecific protein is used to induce fever. We have demonstrated by calorimetric methods a measurable increase in the volume flow of blood during fever. This is accomplished by vasodilatation of the collateral vessels in the diseased extremity. The relief of pain by this measure is often the most striking, and the beneficial effect of the temporary increase of the blood supply is evidenced by accelerated healing in the trophic ulcers. We have employed typhoid vaccine intravenously, as suggested by Goodman and Gottesman for the artificial production of fever.

The removal of foci is an entirely empiric procedure as there is no evidence to incriminate them etiologically. A study of the pathology of the disease indicates an infectious or toxic basis and we have followed the procedure of eradicating obvious foci of infection in teeth, tonsils, and prostate.

Intravenous injections of radium chloride (2) have temporarily relieved pain in 70 per cent of cases. Equal results are obtained by the injection of triple typhoid vaccine intravenously (10). The latter is cheaper and more readily available. The original injection should contain 15,000,000 to 20,000,000 organisms and be increased by a similar number at each injection. A chill and an increase of from 2 to 4°F. in temperature indicates a satisfactory response. The injection can be repeated four or five times at intervals of three or four days. No bad effects of this treat-

ment have been observed in approximately 6000 injections in cases of thrombo-angiitis obliterans and chronic arthritis. After several injections the reactions may be slight but after two or three weeks without any injections strong reactions will again be produced.

*Surgery of the sympathetics.*—Lumbar ganglionectomy and ramisection produce definite and persistent vasodilatation of the vessels of the feet when vascular dilatation is obtainable, as demonstrated by Adson and Brown (1, 5). The rationale of the application of this operation in cases of thrombo-angiitis obliterans in which the main vessels are closed is based on two observations: (1) the frequency with which vasoconstrictor intermittent disturbances are observed in this disease as manifested by color changes, such as pallor and cyanosis, which are usually induced by cold, and (2) the quantitative evidence of vasodilatation that occurs in the diseased extremity with increased environmental and body temperature. From these observations, cases of thrombo-angiitis obliterans can be divided into two groups: those with and those without vasomotor spasm of the collateral vessels. A vasodilating type of operation would exert an effect only on the former type of case. The problem consisted in determining the suitable type of case for operation. Following an injection of typhoid vaccine, the oral temperature and that of the feet are noted at fifteen-minute intervals during the periods of chill and fever. When the surface temperature rises to a greater degree than the oral temper-

ature, vasodilatation of the collateral vessels is present (Fig 1). A vasomotor index is obtained by the following calculation: the vasomotor index equals the increase in surface temperature of the foot less the increase in oral temperature, divided by the increase in oral temperature. This indicates a ratio of the amount of vasodilatation to a given rise in the body temperature. Indexes in excess of 1.5 have been considered favorable for operation. Frequently indexes of from 2 to 3 are obtained. Normals show indexes varying from 2 to 10. Fairly comparable increases in the surface temperature of the diseased feet are obtained preoperatively with fever and postoperatively following lumbar ganglionectomy. This question is still under study and the data are at best only approximate.

*Surgery of the extremities (3).*—The choice of the area for amputation depends on the condition of the vascular supply of the extremities. Fingers can usually be successfully amputated regardless of the amount of obliteration in the ulnar or radial arteries. In this series the disease was never sufficiently extensive to require the amputation of hands or arms. Toes can be successfully amputated in only a small group in which the arteries in the feet are pulsating normally and the skin proximal to the toes is not discolored or edematous. The study of a large group shows that incision of toes or removal of toe nails is never successful and always necessitates higher amputation. Amputation below the knee is successful in 80 per cent of all cases of thrombo-angiitis

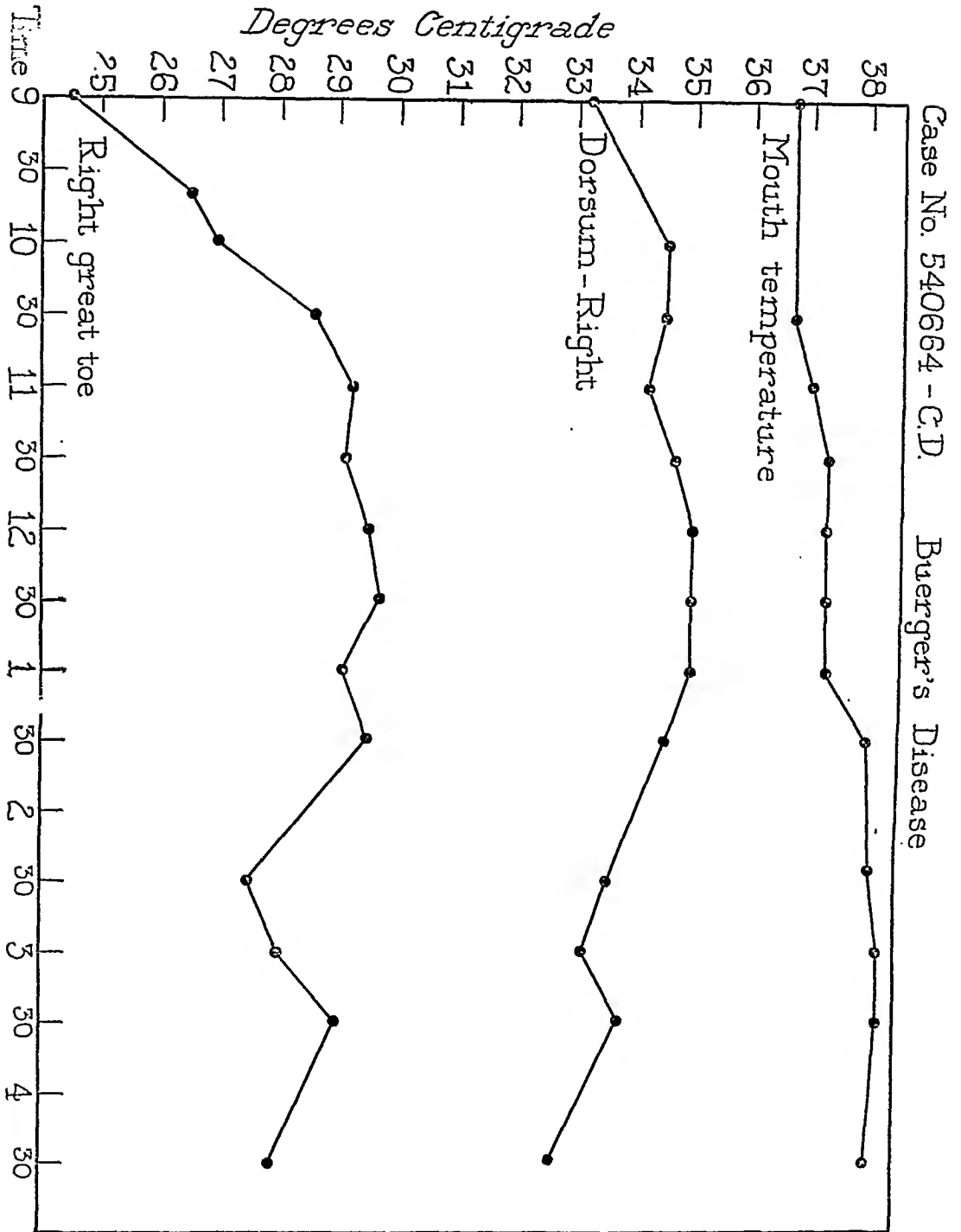


FIG. 1. Foreign protein reaction in thrombo-angiitis obliterans. The skin temperature of the right great toe has increased  $3.5^{\circ}\text{C}$  more than the oral temperature. A comparable increase would probably follow lumbar ganglionectomy.

obliterans regardless of the condition of the pulsations in the popliteal artery provided that the gangrene does not involve the leg and extensive lymph-angiitis or edema is not present. This does not agree with the opinion of other workers who maintain that amputation should always be carried out above the knee. The good result in our series is partially due to the preoperative and postoperative medical care, consisting of the almost continuous application of heat by means of the carbon-filament lamps arranged in an arch over the bed and the intravenous injection of small amounts of foreign protein; both of these measures increase the blood supply of the stump and promote healing. Amputation above the knee should be reserved for cases in which amputation below the knee has been unsuccessful and those in which the patient is unwilling or in too poor physical condition to take the risk of a second operation, if amputation at a lower level has been unsuccessful.

#### PROGNOSIS

The relation of early recognition to the ultimate outlook of cases of thrombo-angiitis obliterans cannot be too strongly emphasized. The presence of gangrene militates greatly against a favorable prognosis but this can be avoided in a great many cases by the early recognition of the disease and the institution of rational therapeutic methods. This can be brought about by the education of the general practitioner and the orthopedist, who see these cases in their incipency. Palpation of the usually pulsating arteries, the circulatory effi-

ciency test, and the recognition of symptoms due to an impaired supply of blood will give the clue to the nature of the disease and usually establish the diagnosis in the early stages. The long period between the first symptoms and the occurrence of gangrene, during which time inadequate or irrational treatment is tried, shows plainly how often the first symptoms are misinterpreted.

Thrombo-angiitis obliterans is apparently a self-limiting disease, as the obliterative process eventually stops. The usual clinical course is not that of arterial insufficiency progressing to gangrene but rather that in which arterial obliteration and the establishment of circulation in the old thrombi and by new collateral channels run hand in hand. The new arterial channels increase with time and eventually the limb will obtain a fair degree of arterial compensation. Trophic changes, as gangrene and ulcers, occur in the stage before arterial compensation is established and when present greatly augment the unfavorable prognosis as amputation is required before adequate new circulation is present. Severe rest-pain adds to the dark outlook as medical measures for relief are unsuccessful in many cases and amputation is required. Edema interferes with healing when small ulcers are present and may prompt a decision to amputate at a higher level as good healing does not occur in an edematous limb. The economic factor has much to do with the prognosis. Patients with inadequate means cannot take long periods of medical treatment, and amputation is frequently

the best solution. Patients with similar symptoms but economically better off can have sufficient periods of rest. The following considerations decide a favorable prognosis: (1) early recognition, (2) persistence with rational treatment to increase the circulation, (3) care to avoid all types of trauma, and (4) impressing on the patient the chronic nature of the disease and the need for constant treatment.

### SUMMARY

Additional experience with thrombo-angiitis obliterans has tended to favor conservative treatment. Close coöperation of the medical and sur-

gical staff have made possible amputations at a lower level and successful healing of trophic lesions. Amputation has been averted in many cases by carefully and persistently carrying out medical and physical measures for long periods. The control of pain by the injection of foreign proteins, and the induction of vasodilatation, by lumbar ganglionectomy in carefully selected cases, have likewise reduced the number of amputations.

The recognition of this disease in the early stages is of utmost importance, as gangrene and similar serious sequelae can be prevented in a large number of cases when the vascular nature of the disease is understood.

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# The Effect of Cholecystectomy On Gastric Acidity\*

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MUCH has been written concerning the influence of the various diseases of the gallbladder on gastric acidity, and it has usually been contended that there is a tendency to lowered acid values in such cases. There are many factors, both physiologic and pathologic, that influence gastric acidity. So true is this that at the Mayo Clinic we have come to regard only the extremes in acid values as significant, and even at these we are inclined to look askance. The physiologic variations may be wide, or certain transient unimportant pathologic processes exert a powerful influence on gastric acidity. Migraine frequently is associated with anacidity, and the same is true of unfavorable psychic influence occasioned by the fear of gastric intubation. Unless there is a more or less constant tendency toward one extreme in any pathologic process it is hardly safe to assume that such a disease is exerting an influence on the gastric secretions. Even the time-honored opinion that anacidity is associated with carcinoma of the stomach is open to skepticism.

Friedenwald corroborated a statistical study made by one of us (2) to the effect that practically half of the lesions of the stomach, proved at operation to be carcinomatous, were found in cases in which free hydrochloric acid was present in varying amounts up to hyperacidity. Clinical records show great variation in free hydrochloric acid values in gallbladder disease. No importance can be placed on this acidity in making a differential diagnosis or in anticipating the intensity of the pathologic change. Diagnostic emphasis has been placed by others on the curve of the fractional analysis in gallbladder disease. It is stated that the curve does not rise but remains low or falls with each succeeding aspiration. This supports the contention of those who maintain that low acid values are significant in gallbladder disease. To our minds the curve of gastric acidity appears to be of no practical value. Extremes in titration values alone are significant. A single aspiration may not reveal this. It is not our purpose in this article, however, to enter into a controversy relative to the value of a single total aspiration as against

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the fractional aspiration as a means of determining the true acid content of the stomach. We wish to report only the effect of cholecystectomy on the acid values. It has been intimated by Rost that cholecystectomy reduces gastric acidity. In speaking of the effects of cholecystectomy he says that there is diminution in the pancreatic secretion, and that "only about one-third of the normal amount of bile plus pancreatic secretion is discharged . . . . This inadequacy of pancreatic and bile secretion in its turn leads to a stasis of food in the duodenum, which reflexly diminishes the hydrochloric acid production in the stomach. This is probably the best explanation for the resulting hydrochloric acid deficiency which now causes numerous general disturbances." DeTakats reports two cases in which lower gastric acids were found after cholecystectomy and cites Hohlweg who reported 83.3 per cent of cases of hypoacidity or anacidity after cholecystectomy. He quotes extensively from the literature and concludes: "The theoretical basis of this procedure (cholecystectomy for hyperacidity) is far from being clear and it is hoped that greater interest in this question may be aroused by this publication." Meyer, Ivy, and McEnery, from experimental work, report, "Our observation, however, would lead us to the view that the removal of the gallbladder per se is not the cause of achylia or anacidity when it occurs."

This study was made in an attempt to prove or disprove by statistical review the impressions regarding the effect of cholecystectomy on gastric acidity. It was decided to compare

the gastric acidity before cholecystectomy to that found after the gallbladder had been removed. One hundred consecutive cases with available data were studied. In some instances a single aspiration of the stomach contents comprised the total observation of acid values. In others a fractional analysis was made. When this was done the highest titration available in the series of aspirations was accepted. Thus the highest preoperative values of acidity, whether from fractional or single aspirations, were used and similar readings of postoperative estimations of acid were compared with these. The postoperative analyses were not made shortly after the operation. In some cases the postoperative titrations were carried out two years after the operation. There is a possibility of extreme variations in the curve of any fractional analysis or in single aspirations under circumstances thought to be constant. This instability of gastric titration values must necessarily somewhat limit the usefulness of this report. The average result of a series of cases, however, should be of some value.

The continuous line shown in Chart I represents the curve of the amount of free hydrochloric acid in these 100 cases arranged in sequence of increasing titration values. Each block represents the acid value obtained in one case. The interrupted line represents the tabulations of the postoperative acidity as compared with the preoperative acidity in each case. Every perpendicular column, therefore, includes two readings, one the preoperative acidity and the other

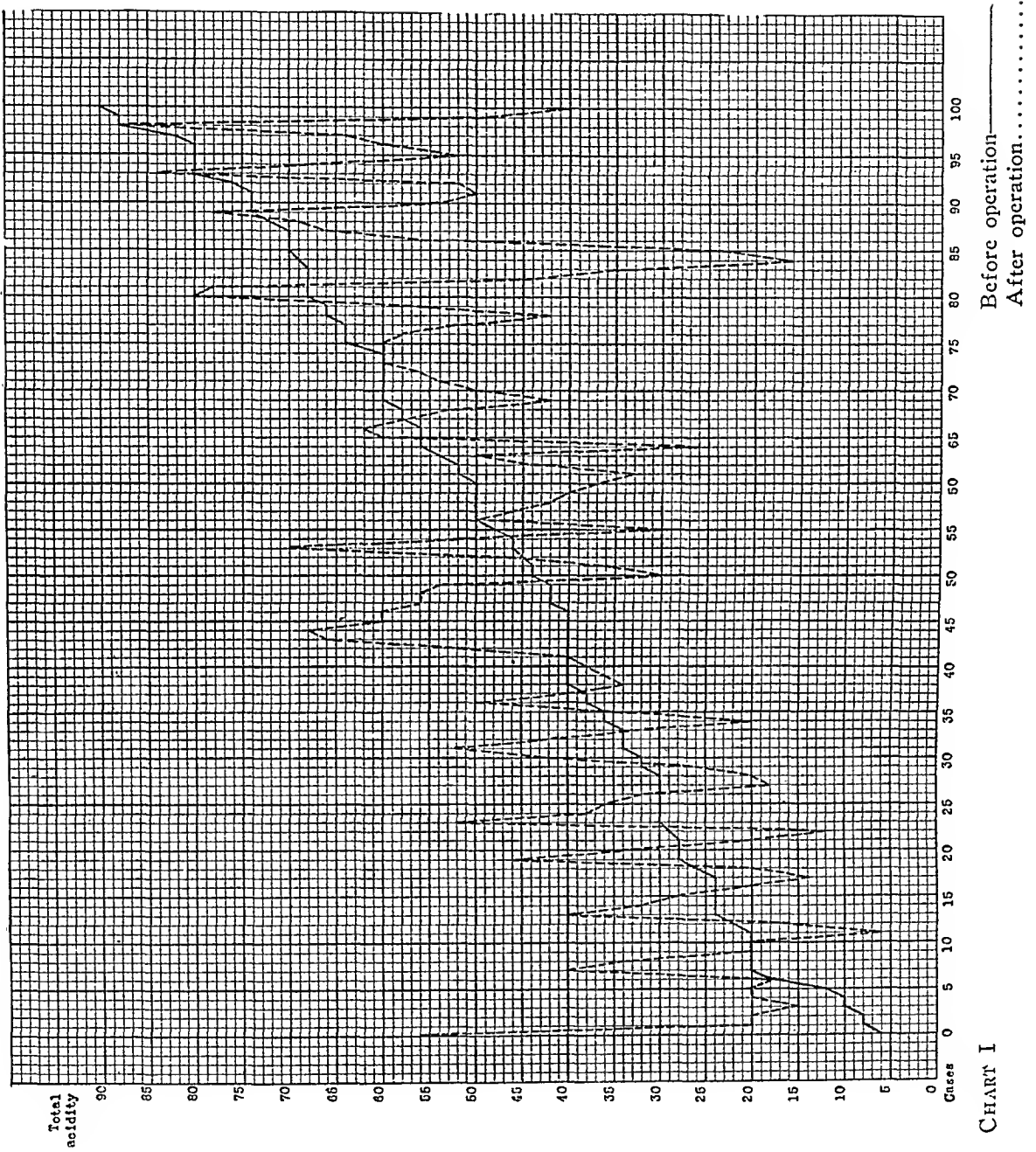


CHART I. Gastric acidity before and after cholecystectomy, arranged according to the increasing acid values of the preoperative acidities.

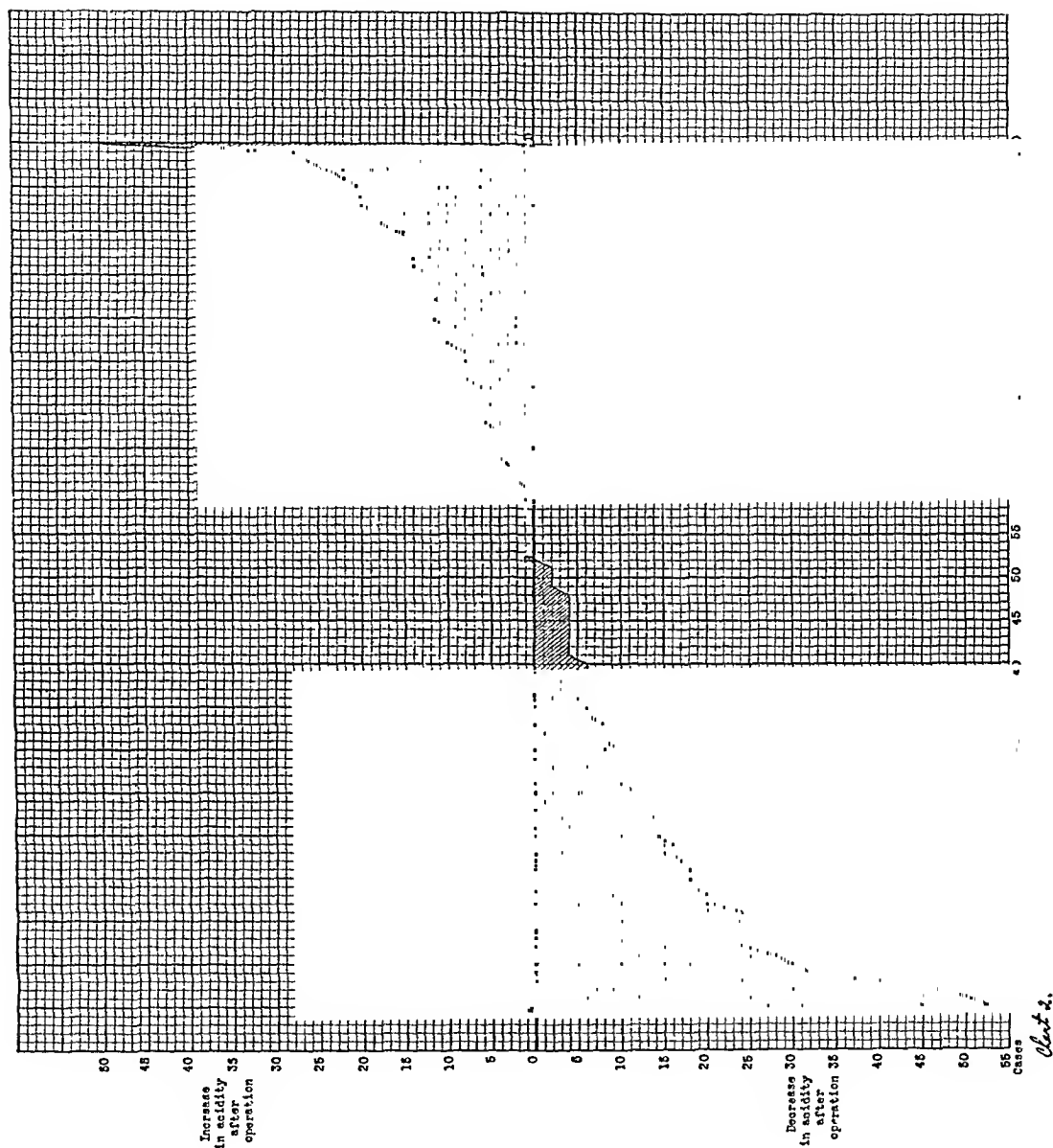


CHART 2. Decrease and increase in gastric acidity after cholecystectomy; shown from a base line.

the acidity obtained some time after the gallbladder has been removed. To illustrate, in the first case the preoperative acidity was 6 and the postoperative acidity was 56. In the second case the preoperative acidity was 8 and the postoperative 20. It has already been mentioned that the conclusion reached is that the acid values are low in cholecystic disease. Chart 1 shows, however, that in 38 per cent of the 100 cases the free acid values were evenly distributed from 6 to 40; in sixty-two the free acid values were evenly distributed from 40 to 90. The difference of preoperative and postoperative acid values, for increased as well as decreased acidity, varied greatly. The maximal decrease was 53 points (Case 84). The maximal increase was 50 points (Case 1). In nine cases values were identical, as is more clearly seen in Chart 2.

In the second grouping the increase or decrease in acid values after cholecystectomy was charted from a base line (Chart 2). In fifty-one cases the acidity was lowered from 2 to 53 points, with an average decrease of  $15.1 \pm 1.2$ , represented by the portion of the chart marked A B. In nine

cases there were identical values before and after operation as indicated by B C on the chart. In the remaining forty cases, comprising part C B of the chart, there was an increase in the acidity varying from 2 to 50 points, with an average increase of  $13.0 \pm 1.0$ . Thus the difference between the average decrease, 15.1, and the average increase, 13.0, is 2.1. The probable error is 1.56. This probable error obliterates the difference.

From such a study it seems obvious that gastric acidity is not consistently altered in any one direction by cholecystectomy. From a study of averages with the probable error, there is no change in the free hydrochloric acid before and after cholecystectomy. It may be concluded that cholecystectomy does not alter gastric acidity. Exception to this statement may logically be taken when it is considered that the postoperative titrations were taken when the patients were still ill following cholecystectomy, and some pathologic process may have been present to affect the acidity, yet with such an even distribution of increased and decreased acidity after operation the objection would be illogical.

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# The Embryohormonic Relations of the Pituitary Gland to Mesenchymal Tissues

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THE control which the pituitary exercises over the tissues of mesenchymal origin is no less striking than that which the thyroid exercises over the ectoderm (1). In this article I present the clinical and experimental evidence which supports this thesis.

From the mesenchyma are derived the following tissues:

1. Connective tissue.
  - (a) Bone.
  - (b) Cartilage.
  - (c) Dentin and cementin of teeth.
2. Lymph glands.
3. Spleen.
4. Blood vessels.
5. Blood.
6. Fat cells.
7. Smooth muscle.
8. Renal cells.
9. Suprarenal cortex.

It is to be emphasized that the pituitary gland itself is not derived from the mesoderm but is an ectodermal tissue and as such is influenced by the thyroid gland which has a selective action on ectodermal tissues (1).

Calling to mind the tissues of mesenchymal origin, it is easy to understand the symptomatology of pituitary

disease. Proof of this selective action will go far toward the understanding of endocrine relationships and the interpretation of diseases involving signs and symptoms which arise from the mesenchymal tissues.

We will now discuss seriatim, the tissues involved in pituitary disease. It is quite obvious that all the data concerning each individual tissue cannot be submitted in a single article. Hypopituitarism exemplifying hypopituitary function, serves the purpose of illustrating mesenchymal tissue relationships. The earlier in life this hypopituitarism manifests itself, the more marked is the mesenchymal tissue involvement and the greater its non-development. Some of the mesenchymal tissues are involved to a greater degree than others, bearing the brunt of the effect. As previously emphasized this can be understood on a basis of constitutional inheritance characteristics. (1)

Degenerative changes with hypofunction will uniformly be found in the mesenchymal tissues in hypopituitary states.

*Connective Tissue.*—In hypopituitarism the connective tissue is not well developed. This condition is

well-known in the Froehlich type of hypopituitarism.

*Bone and Cartilage.*—Beck (2) says that one of the important functions of the pituitary gland is to stimulate connective tissue growth, especially that of bone. Hypophyseal insufficiency, therefore, leads to undergrowth and defective skeletal development. X-ray studies of the terminal phalanges generally show persistent epiphyseal lines. These marked changes in the osseous and cartilage systems in pituitary insufficiency early in life frequently results in dwarfism. The development of the bone nuclei is markedly delayed. Because of this relationship of the pituitary and bone development, it is natural to assume a pituitary etiology for many bone diseases. Osteogenesis imperfecta is believed by some to be due to pituitary insufficiency. Bauer (3) studying the changes in osteogenesis imperfecta, noted that all mesenchymal tissues, such as bone, cartilage, blood vessels and hematopoietic organs were affected. Chondrodystrophy and the progressive muscular dystrophies are other examples of affections limited to mesodermal structures, Bauer (4a) believes that a constitutional anomaly is usually present in these diseases explaining in this way that infantile hypopituitarism does not give the characteristic picture of an idiopathic bone fragility. Denker (5) believes that the bone changes in otosclerosis are due to pituitary disturbance. It will be remembered as noted in the previous article that the mesodermal bony labyrinth surrounds the epithelium of the labyrinth.

Keith (6) believes that the anterior lobe of the pituitary renders osteoblasts hypersensitive to the various stresses which fall on the human skeleton during life. It is interesting to speculate concerning the influence exerted by the pituitary on racial characteristics, particularly the osseous development in racial pygmies and giants.

In the later stages of the growing period growth may suddenly become arrested and the infantile changes are permanent, the epiphyses remain united and so the long bones are underdeveloped.

The larynx also does not mature, males having and retaining a puerile type of voice.

The influence of the pituitary on bone and cartilage development is generally accepted and unquestioned.

*Dentin and Cementin of Teeth.*—The dentin and cementin of the teeth are poorly developed or not at all present. Engelbach and Tierney (7) have emphasized these changes in the dentin and cementin. Ridging and hollowing are frequent.

Experimentally induced hypopituitarism in young dogs produces a persistent first dentition. Bauer (4b). Wheelon (8) discusses at length hereditary and endocrine influences on the congenital absence of the upper lateral incisor teeth. The first two cases were apparently hypopituitary, the third hyperpituitary with widely spaced teeth and absent lateral incisors but from the evidence Wheelon presents, this case shows signs of a lessened pituitary function, (loss of libido, weakness). He concludes that

apparently congenital defects of the upper lateral incisor teeth are rather common.

In Simmond's disease (cachexia hypophyseopriva) loss of teeth is very frequent.

*Lymph Glands.*—The lymph glands are small and hypoplastic in hypopituitarism. The hypoplastic lymph glands are no doubt related to the hypoplasia of the whole hematopoietic system (bone, spleen, blood vessels etc.) The hypopituitary individual not infrequently has enlarged lymph glands with "exhaustion centers" in the lymph nodes.

*Spleen.*—As previously mentioned the spleen partakes in the hypoplasia of the hematopoietic system. Falta (9a) describes the small spleen seen in pituitary insufficiency.

*Blood Vessels.*—The blood vessels are hypoplastic in hypopituitarism. This applies to all three coats. These individuals bruise very easily, slight injury such as a slap on the arm, produces a hematoma.

The work of Krogh (10) is of interest in this connection. From experiments on frogs, he suggests that the normal function of the pituitary hormone is to maintain the capillary tonus. This work emphasizes the position he took with Harrop and Rehberg (11) that the pituitary constantly secretes a substance which circulates in a low concentration and maintains the tonicity of the capillaries. This is important in relation to hypertension, arteriosclerosis, arteritis and other blood vessel disturbances.

Hypotension is the rule in hypopituitarism. Bloch (12) assumes from data at hand, and from therapeutic results with pituitary extract that endarteritis obliterans is caused by lack of pituitary substance.

Kopf (13) found in three patients with Raynaud's disease that injections of "hypophysin" resulted in almost immediate relief of the cyanosis.

Pribram (14) found an enlarged sella turcica in Raynaud's disease. Pituitary preparations were used with marked success and it was deemed probable that pituitary extract exerts a regulating influence upon blood vessel tone.

It has been demonstrated by Weed (15) that the pia-arachnoid (blood vessels) is developed from the mesenchyma and its importance in the formation of cerebro-spinal fluid has been established. Weed and Cushing (16) show that pituitary extract produces an increase of cerebro-spinal fluid. Use of this fact has been made clinically for the relief of lumbar puncture headache.

Cassirer (17) cites a list of observations of coincident Raynaud's and pituitary disease. Henius (18) noted the disappearance of capillary spasm following the use of pituitary treatment in a case of pituitary tumor with Raynaud's disease. Bloch (12) cites a case of Raynaud's disease with pituitary involvement which was benefited by pituitary injections. He believes that all cases of Raynaud's disease should receive pituitary injections.



*Blood.*—If the blood as a whole is related to the state of the pituitary, then hypopituitarism should result in a lessened blood volume and a lessening of the blood elements.

Brown and Keith (19) conclude that the circulating blood and plasma volumes, when compared to body weight are smaller in obese, (hypopituitary)?, than in normal persons. The fat metabolism is slowed through lack of pituitary secretion and therefore the hypopituitary individual *stores* his fat instead of burning it up. Reference is made here to the fact that the fat cells are mesenchymal in origin and intimately linked with the state of the pituitary gland. The obesity of hypopituitary individuals is well-known. Collins and Baudot (20) from their work on the guinea pig, believe that if the conditions described are found in other animals, we may conclude that the embryonic pituitary has a hematopoietic function. Watrin (21) found erythropoietic centers in the pituitary of the pregnant guinea pig and he concludes that other conditions than gestation give rise to erythropoietic centers in the pituitary.

It is natural to infer that the pituitary should influence the blood if we note its relation to bone-marrow. The reticulo-endothelial cells are mesenchymal in origin and for this reason the relation of the pituitary to these cells is very important. Cholesterol injected into the blood stream is taken up by the reticulo-endothelial cells. Such cells, called by Aschoff (22), pseudoxanthoma cells, appear with disturbed fat metabolism, as in lip-

emia, diabetes, icterus, xanthelasma and chronic cholecystitis, and suggest a normal part played by the reticulo-endothelial system in fat metabolism. I mention here, this relation of reticulo-endothelial system to blood formation and fat metabolism in order to emphasize the intimate association of all mesenchymal elements. Ainslee and I (23) have shown that injections of posterior pituitary extract into rabbits over a course of ten days increases the blood cholesterol approximately thirty per cent, again showing the relation of the pituitary to lipoidemia.

"The circulating blood contains cholesterol esters in the plasma, while the sterol itself is present in the red corpuscles. Here it is assumed to protect the erythrocytes against the action of hemolytic substances which unless counteracted, might tend to cause anemia through excessive hemolysis" (24).

Cholesterol is believed to be concerned in various immunologic reactions though its functions therein cannot at present be defined. McNee and Prusik (25) have shown that the Kupffer cells (reticulo-endothelial) and not the liver parenchyma manufacture bile pigments.

Injections of posterior pituitary extract increase the coagulation of the blood, and the non-coaguability of the blood in hemophilia is decreased by this extract in vitro, whereas anterior lobe extract has the opposite effect, (26-27). This may be, however, a tissue coagulin effect.

Hypopituitary individuals are anemic. This is agreed upon by most authors, (Falta, (9b), Biedl, (28),

Bauer, (4c) and many others). These are the "pasty" looking individuals whose appearance probably results from a combination of blood, lymphatic and obesity factors.

*Fat Cells.*—Hypopituitary states result in a lessened metabolism with consequent increased deposition. Experimentally induced hypopituitarism also results in lessened fat metabolism with increased fat development.

The thought suggests itself that an increased pituitary secretion over a period of time would result in increased blood cholesterol and may be an etiologic factor in diseases involving cholesterol metabolism. Ainslee and I (29) have attempted to show that diseases involving cholesterol metabolism such as diabetes mellitus, atherosclerosis, certain types of nephritis, cholelithiasis and others, have important relations to states of pituitary hyperfunction and exhaustion.

Coope and Chamberlain (30) found that injections of posterior lobe extracts (using rabbits and rats) is followed by a well-marked increase in the amount of fatty acid in the liver.

Raab (31) found that the high blood fat of starving dogs was reduced through injections of "pituitrin" and pituglandol." This shows that the pituitary aids the cells in utilizing fat.

*Smooth Muscle.*—Perhaps the easiest way to show the selective action of pituitary secretion on smooth muscle is through the pharmacologic action of posterior lobe injections. This is such a well-known action that everyone is familiar with it. I need but mention the contractile effect it

has on the smooth muscle of the uterus, bladder and intestines. Zondek (32) found that posterior lobe extract after a preliminary inhibition, caused increased peristalsis of the intestine. He believes that the posterior lobe secretion exerts a regulatory effect on peristalsis. Consequently in hypopituitarism it would be expected that the tonus of the smooth muscle would be diminished. Abel (33) isolated a very pure tartrate from the pituitary which is from 1000-1250 times stronger than acid histaminophosphate. This affects the smooth muscle in very great dilutions.

*Renal Cells.*—Hypopituitarism results in polyuria and not infrequently produces diabetes insipidus. That posterior pituitary extract has an effect on renal cells is well-known. Whether this is a diuretic effect or antidiuretic is not yet settled. No doubt dosage, purity of the product, the state of the renal cells, and other factors account for the differences. The concern here is that the renal cells are affected by pituitary secretion.

In diabetes insipidus posterior lobe extract has an antidiuretic effect if lessening of the urinary output is assumed as showing this. An apparently paradoxical situation is present. If the pituitary hormone is essential for proper renal function, then its lack, such as in diabetes insipidus, would result in renal cell hypofunction with water and mineral salt loss. These are essential to body economy. Injection of the hormone stimulates the renal cells to activity with a consequent retention of water and minerals, in other words antidiuresis is

produced. That the action of posterior extract is on the renal epithelium and independent of the systolic pressure has been proven by Hoskins and Means (34).

Skubiszewski (35) studying the micro-physiology of the pituitary in connection with polyuria, in parenchymatus idiopathic nephritis, came to the conclusion that the polyuria may be referred to the pituitary. There is a relation between an increase of basophil leucocytes with deep penetration in the posterior lobe of the pituitary and hyperfunction of these cells. He believes that hyperfunction of the pituitary is responsible for the polyuria. It might also be due to the failure of the tubules to concentrate the urine and this again might be a result of pituitary depression. Falta (9e) says that the polyuria may be referred to a temporary irritation of the posterior lobe through a growing adenoma of the anterior lobe. This conception, he says, may explain the fact that such polyurias also frequently occur in tumors of the hypophysis of other sorts that are associated not with phenomena of hyperfunction of the hypophysis but on the contrary with those of insufficiency. It is evident that polyuria is found in hypo and hyperpituitarism.

Berblinger (36) studying the pituitary in nephritis found a distinct increase of basophil cells in the pituitary in 66.7 per cent of nephritics and an appreciable increase in 31.1 per cent. Hoeppli (37) also verified this basophilic increase. This may be an effort toward compensatory hypertrophy.

Jungmann and Zondek (38) believe that in the condition known as habitual

oliguria, the pituitary gland plays a leading role.

The concentration of chlorides in the urine is greater while pituitary extract exerts its effect; this effect is primarily renal, changes in the blood are secondary, (Fromherz (39).)

McFarlane (40) believes that the pituitary accelerates resorption from the tubules by direct action on tubular cells and not by any vascular change.

Starling and Verney (41) found that in dogs, posterior extract, through its action on the kidney, produces an increase of chloride excretion and a decreased water output. Noguchi (42) experimenting with frogs also found this to be true.

Biedl (28) quoted Ide to the effect that the pituitary is an older sister of the genito-urinary apparatus. It has been shown that apituitarism is associated with aplasia of the suprarenal cortex and mal-development of the genito-urinary tract.

Lathrop (43) reports a case of renal dwarfism in which there was a marked retardation of development of the epiphyses, especially at the wrist. The kidneys were both distorted pieces of tissue which externally hardly resembled kidneys. No mention is made of the state of the pituitary. Some of the symptoms while possibly due to the malfunction of the kidneys, are suspiciously like hypofunction of the pituitary, viz. late onset of menstruation, no secondary sex characteristics, polydipsia, polyuria, dwarfism, retardation of ossification. Even the drowsiness, while most likely renal in origin, is like pituitary narcolepsy.

Freund (44) has reported a case of brain tumor in the region of the pituitary, that had a very high blood nitrogen, (270 mgm.) At autopsy no kidney lesion was found. This case illustrates the fact that depressed tubule function might be expected to result from interference with pituitary function.

*\*Suprarenal Cortex.*—The suprarenal cortex is developed from the coelomic epithelium of the mesoderm in contrast to the medullary portion which has its origin in the sympathochromophil tissue of the ectoderm.

In hypoplastic states of the pituitary, hypoplasia of the suprarenals is found. Total aplasia of the suprarenals is found in anencephaly, hemicephaly, and other failure of brain development. Ziegler (45) cites several cases of anencephaly and hemicephaly associated with aplasia of the suprarenals. Zander (46) noted that the suprarenals were hypoplastic only in defects of the anterior portion of the brain. This is because the anterior cerebral defects include the pituitary gland, which would, therefore, account for the suprarenal defect.

Why would there be any difference between anterior and posterior brain defects?

Kohn (47) believes that the suprarenal hypoplasia is secondary to changes in the pituitary. Defects are found in the infundibulum and pars

nervosa. The epithelial portion also shows changes. There is scarcity of oxyphil and large basophil cells.

Browne (48) studied five anencephalic fetuses. He was struck by the constancy with which the thymus, suprarenals and ovaries were involved in association with the anencephaly. Commenting on Browne's work an editorial in the *British Medical Journal* (1920, 2, 828) says: "The most rigorous search on the basis crani of his anencephalic fetuses showed absolutely no trace of a pituitary gland. The syndrome consisting of protruding tongue and eyeballs, nasal aquilinity, obesity, thymus hyperplasia, suprarenal and genital hypoplasia and stunted growth of body and limbs, agrees in the main with the features of what are called hypopituitarism and apituitarism." (See also in this connection Niemann's Disease, Christian's Syndrome, Paget's Disease of the skull, etc.)

Barlow (49) from his study of four anencephalic fetuses could not verify the absence of the pituitary. It must be noted however that apituitarism is present when the anterior portion of the brain is involved. In Zanders 43 cases of anencephaly the suprarenal defect was present only in those cases which include the anterior portion of the brain. We may conclude that in those cases of anencephaly which include the pituitary gland these are the ones in which the suprarenal cortex is hypoplastic. It is apparent that some anencephalics do not have apituitarism and therefore do not show the syndrome completely. Barlow's four cases were probably of this type.

\*Some of the remarks on the suprarenal cortex are taken from a previous article.

Moehlig, R. C. The Selective Action of the Suprarenal Cortex Secretion on Mesothelial Tissues. *Am. J. Med. Sc.* 168, Oct. 553-565, 1924.

Covell (50) whose work was done on 32 fetuses summarizes from his studies as follows:

1. An hypophysis is present in anencephalic fetuses.

2. It is extremely variable in weight. If the weight is corrected for vascularity, it is usually less than the weight of the normal fetal hypophysis which has also, been corrected.

3. The pars nervosa is lacking in the majority of cases. When present its relative and absolute volumes are considerably less than those of the normal.

4. The pars intermedia is variable in both occurrence and volume.

No mention is made of the state of the suprarenals and this is of prime importance in the matter under discussion.

Ballantyne (51) described 45 anencephalic fetuses and states that the pituitary rarely occurs. Schwalbe (52), Haberfeld (53), and Wrete (54) found the pituitary to be present. Mausch (55) also found it to be present but abnormal, some of the pituitaries consisting only of two lobes.

Bauer (4d) says that it is still undecided whether the brain development suffers because of suprarenal non-development with consequent lack of lipid substance for brain development or whether as Zander maintains with Thomas, that the anterior portion of the brain is essential for suprarenal development. My position is that the anterior part of the brain involves the pituitary with the resulting suprarenal involvement.

The pituitary and suprarenal cortex relationship is important because both are of prime importance in lipid metabolism.

We may conclude that in anencephaly there is a varying amount of pituitary pathology which is often associated with concomitant suprarenal cortex involvement. In the following paper of this series, the suprarenal cortex will be shown to have selective action on mesothelial tissues of which the sex glands and skeletal muscles are important components. It will be readily understood from this that pituitary hypoplasia with suprarenal hypoplasia would result in sex gland and skeletal muscle hypofunction. This is well borne out clinically in pituitary insufficiency with the well marked sexual underdevelopment and muscular fatigue.

*Hyperpituitarism and the Mesenchymal Tissues.*—The mesenchymal tissues show evidence of increased activity in hyperpituitarism. It is emphasized that not all the evidence which favors the selective action of the pituitary on these tissues will be submitted. This would merely be a monotonous repetition.

*Connective Tissue.*—The connective tissue in hyperpituitarism is definitely decreased. Connective tissue increase in the internal organs is found in acromegaly. Small and large fibromas and warts are frequently seen in acromegaly (Bauer, 4e). The combination of acromegaly with Von Recklinghausen's neurofibromatosis is seen very frequently.

*Bone.*—Everyone is familiar with the increased bone deposition present

in hyperpituitarism. The bone changes in gigantism and acromegaly which form such an important part of the clinical picture are examples. The sites for the muscle insertions are also enlarged. The skull, jaw, breast, spine, pelvis and extremities partake of the bone changes. Bassoe (56) gives the skeletal changes in detail. The characteristic spade hand due to phalangeal changes is also a feature of hyperpituitarism.

*Cartilage.*—Marked changes in cartilage formation of a hyperactive nature are the rule. Due to the cartilaginous overgrowth of the larynx, the voice becomes very deep and resonant; this is also true of the female. Zondek (57) cites a case of a woman whose voice was soprano before the onset of acromegaly and became a bass voice after the onset. Jackson (58) gives a detailed description of the laryngoscopic appearances in four acromegalic individuals. The cartilages of the ears, nose and ribs also enlarge. Achondroplasia is probably associated with pituitary disturbance.

*Dentin and Cementin of Teeth.*—In hyperpituitarism the dentin and cementin of the teeth is very well developed. Engelbach and Tierney (7) emphasize the development of the dentin and cementin of the teeth in hyperpituitarism.

*Lymph Glands.*—General lymphoid hyperplasia is found in hyperpituitarism. Bauer (4f) is inclined to ascribe the lymphocytosis and eosinophilia of hyperpituitarism to the pituitary. He cites an operative case of acromegaly with 7,300 leucocytes, 44

per cent lymphocytes and 17 per cent eosinophiles. Well pronounced status lymphaticus as found in several autopsies is reported. Goldstein (59) reports a case of acromegaly with lymphatic leukaemia in which there was splenomegaly with lymphomegaly.

*Spleen.*—The spleen is enlarged presenting a definite hyperplasia. Falta (9c) says that the enlargement of the spleen is a partial manifestation of the enlargement of the lymphatic apparatus. In fact the whole reticulo-endothelial system shows evidence of hyperactivity.

*Blood Vessels.*—There is an unanimous opinion among writers concerning the state of the blood vessels in hyperpituitarism, especially in acromegaly. Arteriosclerosis is one of the earliest changes noted in acromegaly. Earlier authors (Klebs, 60; Brooks 60) lay great stress on the changes in the blood vessels which they maintain are among the earliest observed. Bassoe (61) states that there is a general dilatation of the blood vessels with sclerotic changes. Falta (9c) finds that the vascular system in the later stages of acromegaly almost always show changes. A slight grade of arteriosclerosis develops. Microscopical examination shows that the three vascular coats are involved in these changes and that the media becomes poor in muscle fibers. Borchardt (62) also reports arteriosclerosis as a constant change with likewise increased blood pressure often to 200 mm. Hg. or more. Bauer (4c) reports arteriosclerosis. Cholesterinemia is found in nondiabetic as well as diabetic arteritis and in hypertension. Reference is

again made to the previous article on the pituitary and cholesterol metabolism in which this is discussed more in detail, (23).

*Blood.*—In hyperpituitarism an increased blood volume is frequently found. Bassoe (53) says that the blood is often found at necropsy to be increased in quantity. Polycythemia may occur. Certainly in the *early* stages of hyperpituitarism increased blood volume would be expected. One is reminded of the large built individuals of hyperpituitary build who are plethoric, with florid complexion and are candidates for nephritis, hypertension, diabetes and their resulting complications. The eosinophilia that is present in hyperpituitarism is especially interesting. This finding, together with the lymphocytosis is reported frequently.

*Fat Cells.*—From a theoretical standpoint, the fat metabolism would be increased. Hypercholesterinemia is reported. That the pituitary is related to carbohydrate metabolism is well-known and likewise the glycosuria with lessened tolerance in hyperpituitarism is also a well-known clinical fact. Time will not permit further discussion of this important relationship and it is of course so evident that further data for the present purpose is not necessary. The embryonic origin of the islands of Langerhans is not agreed upon. While some state it is mesenchymal in origin, the disagreement does not permit me to include it in the mesenchymal tissues. If true, this would be a most interesting relationship and would help clear up many points in carbohydrate metabolism.

*Smooth Muscle.*—That fibroids (smooth muscle overgrowth of uterus) are very common in hyperpituitarism, is well-known. Smooth muscle overgrowth of the intestines and bladder is reported.

*Renal Cells.*—In hyperpituitarism the renal function should be increased and likewise the kidneys themselves should be enlarged. So it is found clinically. (Falta, 9d.) It is rather tempting to associate an increased posterior pituitary secretion which has existed for sometime with certain types of nephritis. Likewise through its action on blood vessels it may be considered in an etiological role in hypertension.

Draper's work (64) on the human constitution is definitely confirmatory of the selective action of pituitary secretion. Of hypertension patients he says that the changes or increases in the bony skeleton are precisely along the line of increase found in acromegaly or gigantism. Women of a certain constitutional type, whose skulls, mandibles and skeletons display the insignia of a previously increased activity of the pituitary gland, may under the specific stimulus of pregnancy, develop hypertension or nephritis, either transient or permanent. The closeness of the two groups (hypertension-nephritis) in morphological characters and their approximation to the combined hypertension-nephritis series suggest that idiopathic hypertension and some types of nephritis are different expressions of one and the same disease. The interesting fact noted in Draper's remarks is that the three tissues concerned, viz. bone, re-

nal cells and blood vessels, are mesenchymal in origin and it is not surprising that the bone changes in the hypertension-nephritis groups were precisely along the line of increase found in hyperpituitarism.

*Suprarenal Cortex.*—In hyperpituitarism we should find, theoretically, a suprarenal cortex hyperplasia. This is borne out clinically and the association of hyperpituitarism with suprarenal cortex hyperplasia is reported so frequently that it is a generally accepted fact. Falta (9f) says that there is apparently, frequently hyperplasia of the suprarenal cortex. Bassoe, (65) quoting Amsler, Ausch, Eltester and Schroeder, and others, says that the suprarenals have often been enlarged at necropsy. This enlargement is usually confined to the cortex.

Hofstätter (66) found that posterior pituitary extract injections produce suprarenal cortex hypertrophy.

Assuming that there is a suprarenal cortex hyperplasia in hyperpituitarism, then tissues influenced by the cortex would show signs of hyperfunction. As previously mentioned, these tissues for present purposes are the sex glands and skeletal muscle system.

In the early stages of acromegaly, the sex gland function is increased, likewise the skeletal muscles are very large, being commensurate with the large bones. The latter condition shows how well functional changes are correlated in allied tissues for the large heavy bones require large muscles to control them. Engelbach and Tierney (7) say that these individuals have unusual muscle strength and attain it without exercise.

In the discussion of the embryohormonic relations of the suprarenal cortex which will be given in the next communication, it will be shown how intimate the relation is between the mesenchyme and mesothelium.

### CONCLUSIONS

1. The pituitary gland secretion has a selective action on mesenchymal tissues.
2. The suprarenal cortex as a mesenchymal tissue reflects the state of the pituitary gland.
3. Mesothelial tissues, influenced by the suprarenal cortex are likewise influenced by the pituitary gland.

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# The Nature of the Primary Renal Lesion Produced by Lead\*

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## INTRODUCTION

THE work was undertaken for the purpose of determining: (1) The appearance of early pathologic-histological lesions caused by lead carbonate in the guinea pig kidney, (2) The quantity of lead carbonate required to produce demonstrable lesions, and (3) The length of time required for the appearance of these changes.

This investigation was thought necessary, because, as will be seen from the literature, there is a large number of authors, whom I put in the second group, who state that the primary renal lesions in lead poisoning are vascular, and only a few authors (Von Leyden, Legge and Goadby) of this group mention parenchymatous changes as being rare and secondary in importance.

## MATERIAL AND METHODS

The material used in this study consisted of forty guinea pig (*cavia cobaya*) kidneys. Of these thirty-six were poisoned with lead, while the remaining four were used as controls

for fatty degenerative infiltration. The youngest animal was five months old when it entered the experiment, the age of the other older pigs was not exactly known to us. The animals were kept in as nearly perfect hygienic conditions as possible; fresh drinking water was given each day; food consisted of oats, carrots, cabbage, lettuce, and green hay alternately.

The lead carbonate was given per os in small gelatine capsules in varying doses for different series of animals. Some of the animal series and some individual animals, which survived a longer time, passed through the various dosages, some even through all dosages. The beginning dose was 0.03306 gram, followed by gradually increasing doses: 0.03637, 0.06309, 0.075945 and 0.0909 gram. It must be kept in mind that lead probably gives rise to kidney disease only when ingested continuously for a long time; naturally, of course, in doses which are not sufficient to cause death.

The kidneys were removed as soon as the animal died or in other cases several hours after the death. The kidneys were fixed in mercuric chlorid or Zenker's solution for general histological changes, in 10 per cent

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formalin for fat staining, and in absolute alcohol for glycogen for which Best's carmin method was used. The mercuric chlorid fixed sections were stained with haematoxylin and eosin, and fat was stained with Scharlach-R counterstained with haematoxylin, others with osmic acid.

#### GENERAL CONSIDERATIONS

It is very important to emphasize that laboratory animals should be kept in as nearly perfect hygienic conditions as possible. They should have clean quarters, fresh air and sunshine in so far as possible. Fresh water and food should be at the animals' disposal at all times. The food should be so varied as to produce a balanced menu. This the experimental worker should always bear in mind, as it is essential to keep the animals in perfect health. The stock animals should be treated in the same way, because, if not, they are latently ill before the starting of the experiments, and so give erroneous results. Because the animals were not kept in hygienic conditions, some authors have reported pathological findings as occurring in normal, healthy animals. Animals, which show pathological conditions should not be regarded as normal, and experiments should not be carried out on such animals.

A review of the literature on nephritis saturnina and early renal lesions in lead poisoning precedes the account of our own results.

#### LITERATURE

Literature on the pathological anatomy of nephritis saturnina and early

renal lesions in lead poisoning may be classified in *two main ways*: 1. According to the opinions concerning the part of kidney in which pathological anatomical changes begin first. II. According to the opinions as to the type of nephritis produced by lead poisoning. According to the classification of either one of these two ways there are three distinct groups of authors.

I.—If we divide the authors according to the first consideration, we shall find one large group of authors, who state that primary damages are produced in the parenchymatous units, glomerular and tubular epithelium. The second large group thinks that the blood vessels and capillaries are primarily damaged. The third group, however, states that the changes are coordinate and not subordinate to one another; that they are the effect of the same cause, acting simultaneously on different tissues.

II.—Classification according to the type of nephritis produced by lead poisoning shows three main opinions among authors. 1. The largest number of these believe there is first an acute parenchymatous glomerulo-tubular nephritis, followed by chronic interstitial nephritis with secondary contracted kidney (granular kidney). 2. Another group is of the opinion that the nephritis saturnina begins with atherosclerosis of the larger and smaller renal arteries and terminates as primary, or genuine contracted kidney. A few authors of this group mention acute nephritis saturnina with parenchymatous degeneration as very rare. 3. The third group combines the opinions of the two preceding ones.

Namely, like the first group, they too state that there is an acute parenchymatous glomerulo-tubular nephritis saturnina, followed by chronic interstitial nephritis with secondary contracted kidney, but in addition to that claim that there is a complication of the just mentioned picture by damage to the blood vessels, consisting of degeneration of muscle coat, thickening of vessel wall, hyaline degeneration, atherosclerosis or obliteration of lumen. 4. As a fourth group here may be mentioned that there are reported a few instances, where authors found only parenchymatous degeneration in the kidney without any interstitial changes.

Since those who found exclusive or predominant changes in the parenchymatous parts of the kidney with secondary contracted kidney state that the process begins with glomerulo-tubular degenerative changes, and others regard it as primary in the blood vessels, I shall analyze the literature according to the type of nephritis, noting in each group its opinion concerning the primary origin of the process.

*Group I.*—With the exception of Ophüls (34) 1907, and Stieglitz (40), who are of the opinion that the changes in kidneys are coordinate and not subordinate to each other, all other authors of this group think the process begins in the glomerulo-tubular epithelium.

*Bright* (4) noted a connection between plumbism and albuminuria, and contracted kidney, which was confirmed by *Tanquerel des Planches* (42). *Charcot* (6), and *Charcot et*

*Gombault* (7) thought the tubular alterations primary and the interstitial and vascular lesions secondary to these. Albumin was noted only with hematuria. Besides the usual features microscopically they found lime salts in the thin portion of Henle's tubuli and proliferation of epithelium in the tubuli contorti. The final stage of this lesion they called "cirrrose epitheliale" *Maier* (27) thought the character of the damage in chronic lead poisoning was a parenchymatous degeneration with resulting connective tissue induration. *Lublinski* (23) found in the urine of two persons poisoned with lead: albumin, epithelial cells, blood cells, granular cylinders; and he supposed that contracted kidneys existed, but these were not examined. It will be seen from these statements that albuminuria in lead poisoning is reported as conspicuous only in advanced cases, also the finding of blood in the urine by *Charcot et Gombault*, and *Lublinski*.

*Prévost et Binet* (37) say that divers phases of the nephritis saturnina finally terminate in interstitial nephritis with sclerosis, diminution in size of the kidney and very often cyst formation. They noticed yellowish, refractive incrustations, which they thought were lime phosphates. *Oliver* (31), besides parenchymatous degeneration also found fatty degeneration in acute parenchymatous nephritis, and states: "As these are, apparently, the early stages of acute lead poisoning, alike in man and animals, I regard them as characteristic of plumbism." Later he saw what he thought was true interstitial nephritis. *Stieglitz* (40)

reports experiments on rabbits and guinea pigs varying in time from 6 to 241 days. He found parenchymatous changes most often in the tubuli contorti and hyaline degeneration in the glomeruli. Hyaline cylinders were seen mostly in tubuli contorti; in some cases lime salt impregnations. He found also chronic interstitial nephritis with rich increase of nuclei around the tubuli and blood vessels. Arteriosclerosis alone in the kidneys or even in general arteriosclerosis is regarded as rare. He is also an advocate of the coordinate theory of the kidney lesion in lead poisoning. I especially call attention to Oliver's statement, that he regards the parenchymatous and fatty degenerations as the primary conditions occurring in the early stages of acute lead poisoning, because, as we shall see later, I found the same degenerations as the early lesion of acute lead poisoning.

*Paviot* (36) called attention to the frequent occurrence of a productive interstitial nephritis besides all the tubular alterations. *Jores* (19) expresses himself against the origin of the process in the blood vessels and denies any analogy between experimental and human lead nephritis. He saw lime salt deposits especially marked in the guinea pigs. Further he saw parenchymatous changes, lesions of the epithelium, albumin in capsular spaces, hyaline cylinders in dilated tubuli and blood pigment in tubuli (p. 205). Other than small patches, he saw connective tissue growth only in one animal, which lived the longest experimental time (p. 183). He thinks parenchymatous

degeneration may be not the result of a direct action of lead, but perhaps of a general anemia caused by lead (p. 214). His denying of any analogy between experimental and human lead nephritis does not seem very convincing. It should not be forgotten that, while experimental lead nephritis is due only to the lead, this hardly can be said of human lead nephritis, where, besides the lead, practically always some other reason for the nephritis may be found; such as age, alcohol, syphilis, etc. The differences should be considered from the standpoint of the differences in etiology and the final stages of the process as seen in the human cases when examined. His finding of albumin in the capsular space is quite important, because the other authors, so far as I know, do not report such a finding; and because, in a positive case, there arises the question as to the source of this albumin, whether from the blood plasma filtrated through the glomerular wall, or from the degenerating glomerulo-capsular epithelium. To my mind it must be from both sources, because without alteration in the filter epithelium such a quantity of albumin from the blood plasma would not be present in the capsular space; and when this epithelium is degenerated it not only produces waste albumin, but, of course, allows more albumin from the blood plasma to pass, as is pointed out by *Cushny, A. R.* (p. 202) (10). I might add that in some of my cases there was precipitated albumin in the capsular space. Regarding the indirect cause of the degenerations, there are contrary opinions, as for example *Legge* and *Goadby*, who think that the

primary lesions are due to direct action of lead poison.

*Kobert, R.* (21) speaking about Phosphor, Plumbum and Alcohol poisoning says: "Die Nieren sind bei akuten Vergiftungen meist geschwellt, während sie bei chronischen cirrhotisch verkleinert sein können. Auch Verfettung, Embolisierung und multiple Blutaustritte sind nicht selten." In experimental animals he did not find any distinct cirrhosis of the kidney; interstitial or parenchymatous inflammation is seen.—In my opinion this may have been due to insufficient length of time for definite cirrhosis to develop.—He says that no metallic poison has so characteristic an effect on the kidney as lead. The excretion of even small quantities exerts an injurious action on the cells of the parenchyma, destroys them and eventually sets up a true cirrhosis.

*Ophüls, W.* (34) experimented with guinea pigs and dogs. Those animals which lived for a comparatively shorter time, about 2-6 months, showed only parenchymatous degeneration, necrosis and desquamation of epithelium of tubuli contorti and ascending part of Henle's loop. Usually he found regenerative evidence in this epithelium. In some cases pigmented epithelium, and occasionally slight fibrosis of the glomeruli and slight thickening of the glomerular capsule were found. Sometimes he found casts, but they were not very numerous. In animals which lived 1-3 years, he found "marked chronic interstitial nephritis," actual granular kidneys with narrow cortex, collapse of tubuli over large areas, marked intertubular fibro-

sis and casts. In the urine of dogs he was not able to find either albumin or casts and writes: "This observation gives support to the clinical suspicion that in man also such lesions may develop with very little, if any, change in the urine." No calcareous infarcts were found in these kidneys, and no vascular lesions of the aorta or in branches of renal arteries. He states that this nephritis does not resemble human nephritis, but is comparable to experimental uranium nephritis. He is an advocate of the coordinate theory of commencement of the renal lesion and rejects the subordinate theory (1907). It will be noted that Ophüls did not find many casts in the kidneys of guinea pigs, and neither albumin nor casts in the urine of dogs; as will later be seen I also found but little albumin and few casts in the urine of my experimental animals. Further, since it seems an important fact, if true, attention is again called to his statement regarding the clinical suspicion that in man such lesions, without urine changes, also may occur.

*Ryle* (39) reports concerning the wife of a tinsmith who for a long time washed her husband's clothes. He found chronic interstitial nephritis, small contracted kidneys with granular surface. Microscopically very little remaining kidney substance was found. Urea content of the blood was 2.46 grams per 1000 ccn, or eight times the normal amount. He thinks the female is more susceptible to lead than the male. *Rathery et Michel* (38) report the instance of a woman who took small doses of lead subacetate for fifteen days. The authors



found the most important lesions in the tortuous and collecting tubuli. Besides parenchymatous degeneration, necrosis and desquamation of the epithelium of the tubuli contorti, collecti and ascending parts of Henle's loops, they found intraglomerular hemorrhages with some round cells, proliferation and hypertrophy of the cells of the Bowman's capsule, which were pear shaped or elongated, and certain of these cells were filled by fine granules. A large proportion of the straight tubules were packed with granules from the tubuli contorti and, being already damaged, became completely impermeable. In the interstitial tissue, around glomeruli and straight tubuli, there was found round cell infiltration. This case is in contrast to the opinions of MacCallum, Legge and Goadby, and other authors from the second group, who base their opinions upon the human cases, and say that acute lead poisoning is rare (MacCallum), and only after large doses (Delafield and Prudden, F. C. Wood). *Aub. Fairhall, Minot and Resnikoff* (2) are of the opinion that chronic nephritis, supposed to be caused by lead, presents the picture of the typical secondary contracted kidney. *Gwyn, B. N.* (15) says: "A slight degree of albuminuria with some casts is not uncommon in the early stages, especially if the dosage has been large. Albumin and casts are frequently present during an attack of colic. After prolonged poisoning progressive chronic renal changes may become the most important feature of the case." According to my knowledge the findings of the authors of this group, who

found as early renal lesions parenchymatous degeneration and fatty degeneration infiltration with swollen kidneys, and as chronic lesion secondary contracted, or granular kidney, are very logical and most probable. It is also important for the prognosis of the kidney disease of such a nature that several authors noted the regeneration of the tubular epithelium.

*Group II.*—This group of authors is of the opinion that the nephritis saturnina starts with primary changes in the blood vessels and terminates as a primary, or genuine contracted kidney.

According to *von Leyden* (44) lead nephritis is identical with Virchow's atrophic granular kidney, or what he terms sclerotic atrophy, or what he In these the tubuli are diminished and partially tortuous, the interstitial connective tissue is increased and full of nuclei; the afferent and efferent vessels as well as glomerular loops show exquisite hyaline degeneration. The glomeruli are contracted, shiny and homogenous. The intima of the larger vessels is very hypertrophic. His patient always had albuminuria. He thinks that parenchymatous degeneration is rare. According to *Gayler* (12) arteritis of the smallest arteries, which commences in the muscular coat, followed by endarteritis and obliterative arteritis, is the preliminary damage in lead kidney. *Strümpel, A.* (41) says the kidney of plumbism is the "genuine contracted kidney," extremely slow and chronic, but with constantly progressive atrophy of renal parenchyma and its substitution by cicatricial tissue. *Gull and Sutton* (14) have de-

scribed arteriocapillary fibrosis with great hypertrophy of the intima of the larger vessels. *Legge and Goadby* (22) state that lead nephritis is not acute, but of chronic cirrhotic type, which requires a long time for development; in animals two years. In the earliest cases interstitial nephritis is present, later changes in the glomeruli and fibroid degeneration take place, but even in this early stage interstitial hemorrhages without hematuria are present; the venules rather than the arterioles appear to be first damaged, intima being first affected, resulting in extreme narrowing and blocking of the vessels. "Parenchymatous nephritis may be seen, probably resulting from the transudation taking place from the vessel walls." It is interesting to point out so many "interstitial hemorrhages" only, always without blood in glomeruli or tubuli, and, naturally, without hematuria. The absence of hematuria, taken in connection with their plates, is not very convincing regarding interstitial hemorrhages. Their illustrations look more like a simple congestion. *Castex, M. R.* (5), according to clinical symptoms, thinks that there developed chronic interstitial nephritis, granular kidneys, on a vascular (arteriosclerotic) basis. He found albumin, epithelium, leucocytes, erythrocytes, hyaline and granular casts, and increased urea present. *Machwitz und Rosenberg* (26) are of the opinion that saturnismus plays an important role in the etiology of "malignant kidney sclerosis." *Mallory* (28) says: "Lead poisoning is often blamed for vascular (arteriosclerotic) nephritis. *Delafield and Prudden, F. C. Wood* (11) are of the opinion that

acute lead poisoning is present only with large doses and that in such case there may be fatty degeneration of the renal epithelium. In chronic lead poisoning kidneys are arteriosclerotic. *MacCallum* (25) thinks that acute lead poisoning is rare, and that chronic poisoning produces diffuse nephritis of the arteriosclerotic type. *Newburgh* (29) says chronic lead poisoning produces primary contracted kidney. He is also an advocate of the coordinate theory of lesion of the kidney. *Hamilton* (16) writes: "According to most authorities the underlying pathology of chronic lead poisoning is a structural change in the blood vessels (p. 20). The proliferative endarteritis is probably reparative and compensatory to the damage done to the muscular coat" (p. 22). According to her, in the subacute form of renal plumbism, changes are mixed; not only a thickening of the vessels with occlusion of the lumen, but a marked degeneration of the convoluted tubuli. On page twenty-nine of her book she quote: 'Volland (54), Mohr (55), and Stachelin (56),' but in the papers of the three authors, quoted in her bibliography, there is not a single word about either kidneys or about lead poisoning.

The important fact of the literature brought out by this group of authors is that they all state that albuminuria and vascular lesions are characteristic for lead kidneys, which, it appears to the writer, is due to the fact that they report, as well as the clinicians, their opinions concerning human cases, which obviously were chronic, for they showed distinct albuminuria and vascular lesions, which is not charac-

teristic for early lesions of lead kidneys. In such chronic human cases of lead poisoning, where albuminuria and vascular lesions were constant, they surely found hypertension and other symptoms of renal-cardiovascular changes, which, however, may not be due alone to the lead poisoning, but to the age of patients and to some other cause of renal-cardiovascular lesions, such as alcoholism, syphilis, and some other toxicosis or infection.

It is interesting that the authors of the second group, who are of the opinion that the primary renal lesions in lead poisoning are the vascular lesions, with the exception of Legge and Goadby, do not report experiments with lead poisoning, and Legge and Goadby, who do report experiments on cats, write: "Parenchymatous nephritis may be seen...." differing from the first and third group in that they place in the first rank, as most characteristic, "interstitial hemorrhages."

*Group III.*—In the third group have been placed those authors who believe the primary changes are of parenchymatous character, but that that there are also secondary vascular changes.

Here belong: *Cornil et Brault* (9), *Hoffa* (18); *Coen, E. e d'Ajutola, G.* (8) who, besides parenchymatous degeneration, necrosis and desquamation, describe glomeruli very rich in blood, proliferation of endothelial cells and epithelium of tubuli contorti, hyaline degeneration of blood vessels and finally interstitial plastic nephritis. Hoffa studied rabbits and guinea pigs, while Coen and d'Ajutola studied rabbits. *Thompson* (43) is of the

same opinion; both he and Coen and d'Ajutola often found albumin and different kinds of casts in the urine. *Oliver* (32) also mentions thickened arterioles as a frequent finding besides acute parenchymatous and chronic interstitial nephritis. *Page* (35) writes: "While it is difficult to deny the possibility of small amounts of lead a directly deleterious action on the musculature of the blood vessels, it would seem that the infliction of an injury on the renal epithelium is the first step in the process. The damaged cells then fail to excrete certain toxic substances from the blood, which being retained cause a rise in blood pressure and in time arteriosclerosis.—the damage is repeated, as also are the attempts at regeneration and repair, so that in time we have the sclerotic or granular contracted kidney." The human cases he reports showed albumin and casts present, also a rise in blood pressure. *Herrick, J. B.* (17) says that long continued action of lead may induce chronic nephritis, both parenchymatous and secondary interstitial, arteriosclerotic and amyloid kidney, and that in chronic intoxications one must assume the condition of the altered blood.

*Group IV.*—Few authors report that they found only parenchymatous or fatty degeneration, without any interstitial change in the kidney. *Anino* (1) studied kidneys of dogs, rabbits and guinea pigs, and, besides parenchymatous and fatty degeneration, found only vacuoles and granular atrophy of protoplasm and hyaline degeneration of nuclei. He did not observe any interstitial changes.—The

explanation of such cases may be either due to the fact that the experimental time was not long enough, or that insufficient amount of lead was used in the experiments.

To obtain a clearer picture concerning albuminuria saturnina the findings of the following authors are of value: *Oliver* (33) in his observation of temporary and permanent albuminuria is of the opinion that albuminuria saturnina is not only functional, but is caused by a lesion of the kidneys. However he found albuminuria in only nine out of thirty-seven cases, that is, only twenty-five per cent. Besides such inconstant albuminuria, he noted anemia, pallor, edema and epileptiform attacks. *Giglioli* (13) says transient appearance of albumin, tube cases and, sometimes, of kidney cells may be the first sign calling attention to the lead poisoning. *Widal, F.* (45) states that plumbism causes Brightism, albuminuria, azotemia and high blood pressure, the consequence of which is encephalopathia. He is discussing human cases.—Finally *Lyon, G.* (24) subjected several rabbits for two or three months to subcutaneous injections of lead acetate, and, although the animals wasted and finally died, the effects on the kidneys were negative.

Further it appears to the writer sufficiently important to emphasize the opinions of *Ophüls*, *Stieglitz* and *Newburgh* that the injuries in the kidneys are coordinate and not subordinate, and that they are the effect of the same cause acting simultaneously on different tissues with varying vulnerability and different reaction time.

In general all the authors of the four groups agree that there are kidney lesions due to lead poisoning. The difference in opinion concerning the part of the kidney, in which the changes begin first, and the type of nephritis produced by lead poisoning, it appears to the writer, are due to the different stages of kidney lesions studied by the various groups of observers. Therefore, while the authors of the fourth group, who carried on their experiments for only a short period, could find no lesions or found only the beginning degenerations, cloudy swelling and fatty degenerative infiltration, the authors of the second group, who studied practically only human cases, dying with advanced lesions and perhaps further complicated with lesions of some other source as age, alcohol, etc., found mostly genuine contracted, or arteriosclerotic kidneys. That such is the case is shown by the fact that several authors of this group, such as: *Von Leyden*, *Legge* and *Goadby*, *Delafield* and *Prudden*—*F. C. Wood*, and *MacCallum*, speak also of parenchymatous degeneration and nephritis although they say "rare" or "may be seen." Review of the literature shows that the writers who state that parenchymatous lesions in the kidney are primary in lead poisoning base their observations upon experimental results in various kinds of animals, while those who believe the primary changes are vascular made no experimental studies, or at least fail to mention such.

According to *Jores* and *Herrick* changes in the lead kidneys are the result of anemia, while *Legge* and *Goadby* say the kidney suffers directly

from the effect of the circulating lead. The writer agrees with the belief of Jores and Herrick, but at the same time one must admit that the latter authors' idea may also be correct.

As the review of the literature shows fatty degenerative infiltration was the early lesion of the lead kidney, noted by: Oliver (31), Kobert, Anino, and Delafield and Prudden—F. C. Wood. It is not difficult to understand this, if one has in mind the nature of poison and marked anemia produced by it. The occurrence of proliferation and regeneration of the epithelial cells, as described by Coen, E., e d'Ajutola, Page, Ophüls W., and Charcot et Gombault, seems logical.

Blood was found in the lead kidneys by *Kleinenberger* (20), *Ockerblad* (30), Jores, Kobert, Coen, e d'Ajutola, Ophüls, and Legge and Goadby (the last two in the interstitial tissue).

It may be noted that *lime salt impregnations* in the kidneys of lead poisoning were seen by Jores, Prevost, et Binet, Charcot, Gombault, Paviot, Stieglitz, and *Beer, E.* (3).

#### EXPERIMENTAL

##### BRIEF DESCRIPTION OF CLINICAL AND PATHOLOGIC-ANATOMICAL FINDINGS

Since the clinical manifestations of all the animals were fairly uniform, a general description of these will suffice to cover this part of the work, and will avoid unnecessary repetition.

The first general symptom shown by the animals after four to five doses of 0.036 gram lead carbonate is increased sensitivity and excitability. At-

tacks of convulsions and symptoms of colic usually begin after a total of 0.2 to 0.4 gram of lead carbonate per os in five to six subsequent days has been given. Some animals will die in these convulsive attacks, others survive. Animals receiving a lesser amount of poison during this period of time, and surviving ones, begin to lose weight and to show anemia, poikilocytosis, anisocytosis, normoblasts and basophilic granules in red blood cells. Although Legge and Goadby (p. 78) state that basophilia is normal in the red blood cells of the guinea pig, my animals showed a distinct increase. The anemia and loss of weight are progressive if the animals are given constantly sufficient doses of lead carbonate to keep them sick, but insufficient to cause death. Later the animals become very emaciated and, when they are very ill, are quiet, depressed and feverish, take little or no food or water, fear noise or any kind of excitement. They die usually in convulsions with cramps in their extremities, opisthotonos or emprosthotonos. In the grave stages of the illness the animals are very weak, show delirium, weakness and paralysis first in hind legs.

The urine of those animals, dying early, e.g., after 0.5 gram of lead carbonate showed traces of slightly more than a trace of albumin, one to two leucocytes, several epithelial cells, and considerable triple phosphate crystals and amorphous salts. The urine of the animals dead after three to five grams of lead shows more albumin, but never a marked amount, the same kinds of cells, crystals and salts, as above mentioned; but never was blood

found in the urine. These are the general clinical findings varying only in degree in different animals according to the time and total amount of lead given.

In this connection it is important to note that in the later period of the experimental time the animals become within certain limits immunized against the lead carbonate, so that they continue to live even though two to four times the original dosage is given, depending, of course, on the period of the experimental time.

The cause of death of the animals is clear. They died usually in convulsions due to the lead poisoning and not from other disease processes.

#### GROSS APPEARANCE OF KIDNEYS

With one exception the gross pathological picture presented by the kidneys was so uniformly similar that a single description will suffice for all. Grossly the kidneys showing fatty degenerative infiltration were increased in size, swollen, with smooth yellowish-white surfaces, in which distinct yellowish streaks and points were visible. Only one showed a finely granular surface, indicating secondary contracted kidneys. This kidney was that of the experimental animal, which lived longest (202 days) and received the largest amount of lead carbonate (7.28018 grams).

#### MICROSCOPICAL FINDINGS

The material is arranged according to the total amount of lead received.

1. Length of experiment 4 days, received 4 doses of 0.03306 gram each. Total 0.13224 gram.

Kidneys show extreme congestion, oedema and several casts. Epithelial cells of Henle's

loops and distal convoluted tubuli are slightly vacuolated.

2. Length of experiment 5 days, received 5 doses of 0.03306 gram each. Total 0.1653 gram.

Kidneys show slight congestion, few casts and very few lime salt deposits in the proximal convoluted tubuli and Henle's loops. There is slight vacuolization of the epithelial cells of Henle's loops and distal convoluted tubuli. Small lesions of spontaneous nephritis in cortex.

3. Length of experiment 8 days, received 8 doses of 0.03306 gram each. Total 0.26448 gram.

The microscopical picture is the same as in No. 2, except for the small spontaneous lesion in the cortex.

4. Length of experiment 10 days, received 10 doses of 0.03306 gram each. Total 0.3306 gram.

Congestion; here and there in the lumen of the tubule precipitated albuminous network. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli are slightly finely vacuolated—probably due to fatty degenerative infiltration.—Slight parenchymatous degeneration.

5. Length of experiment 21 days, received 11 doses of 0.03637 gram each. Total 0.40007 gram.

Microscopically shows congestion, oedema; precipitated albuminous network and few casts in convoluted tubuli and Henle's loops. Some of the proximal convoluted tubuli show parenchymatous degeneration and absence of the nuclei. Epithelial cells of Henle's loops and collecting tubuli are slightly vacuolated. In the papillary part of the Henle's loops there are lime salt impregnations.

6. Length of experiment 21 days, received 11 doses of 0.03637 gram each. Total 0.40007 gram.

Microscopical examination shows congestion, oedema; networks of albumin in proximal convoluted tubuli; small number of casts and depositions of lime salt in Henle's loops. Few lymphocytes in the pelvic mu-

cosa. Moderate cloudy swelling in proximal convoluted tubuli. Slight fatty degenerative infiltration.

7. Length of experiment, total amount, and microscopical picture is the same as in No. 6.

8. Length of experiment 13 days, received 13 doses of 0.03306 gram each. Total 0.42978 gram.

7 doses of 0.06309 gram each. Total 0.44163 gram.

Shows passive congestion, few hyaline casts in Henle's loops and distal convoluted tubuli, some of casts being calcified. One larger calcified body in glomerulus—like space in the cortex. Slight fatty degenerative infiltration.

10. Length of experiment 14 days, received 14 doses (13 of 0.03306, and 1 of

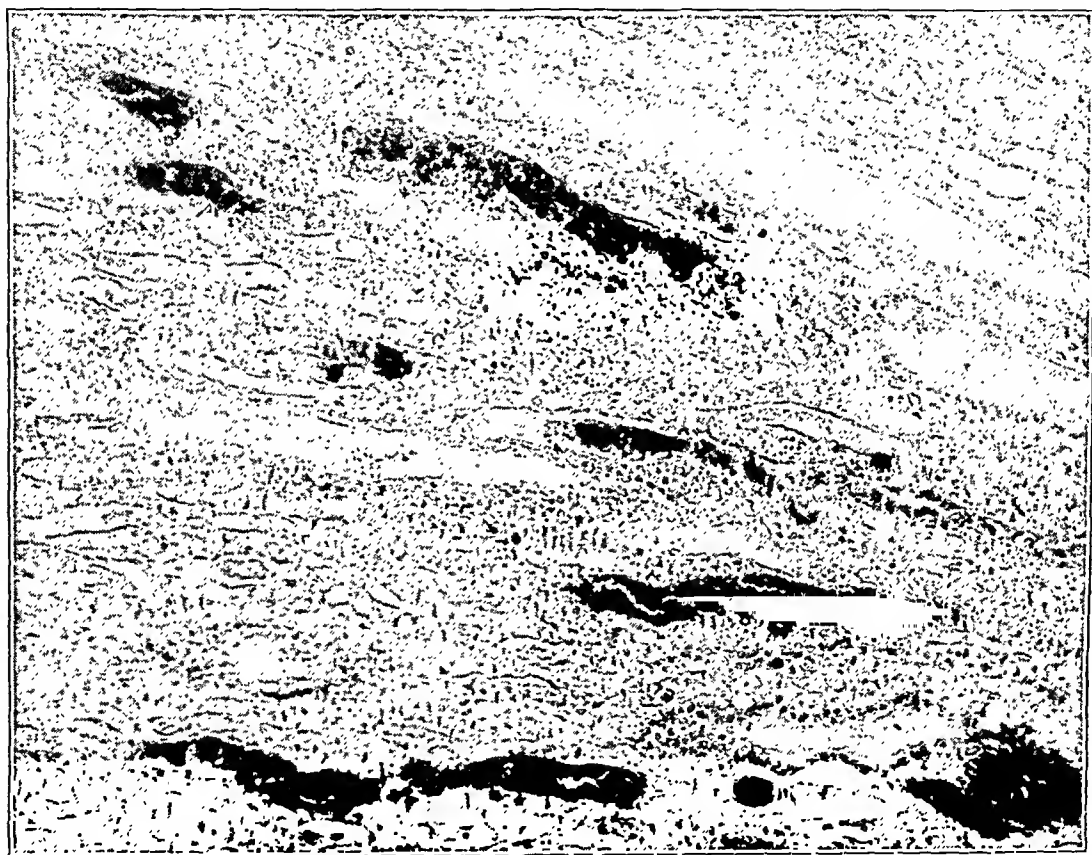


FIG. 1.—From Guinea-pig No. 12. Hyaline casts and lime-salts in thin portions of Henle's loops in papilla.

Microscopically shows congestion, edema, precipitated albuminous network and few casts in the proximal convoluted tubuli and Henle's loops; in these there are few lime salt deposits. Epithelial cells of Henle's loops, distal convoluted and collecting tubuli are slightly vacuolated. Slight parenchymatous degeneration and fatty degenerative infiltration. Few lymphocytes in the pelvic mucosa, indicating slight pyelitis.

9. Length of experiment 15 days, received

0.03637 gram each). Total 0.46615 gram.

Microscopical picture is the same as in No. 9, except for more precipitated albumin and slight pyelitis.

11. Length of experiment, total amount, and microscopical picture is the same as in No. 10, except for the slight pyelitis.

12. Length of experiment 17 days, received 15 doses (13 of 0.03306, and 2 of 0.03637 each). Total 0.56864 gram.

Microscopically shows congestion, little albuminous precipitate, few casts and lime salt deposits, slight cloudy swelling and fatty degenerative infiltration.

13. Length of experiment 8 days, received 4 doses of 0.155 gram each. Total 0.62 gram.

Shows congestion, in some of the tubuli precipitated albumin and here and there a small cast, which in the papilla are impregnated by lime salt. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli show fine vacuoles—fatty degenerative infiltration. Here and there one can find mitotic figures. Slight cloudy swelling.

14. Length of experiment 8 days, received 5 doses of 0.155 gram each. Total 0.775 gram.

Microscopically shows marked congestion, here and there precipitated albuminous network. Epithelial cells of Henle's loops, distal convoluted and collecting tubuli are finely vacuolated, indicating fatty degenerative infiltration.

15. Length of experiment 7 days, received 5 doses of 0.155 gram each. Total 0.775 gram.

Microscopical picture is the same as in No. 13.

16. Length of experiment, total amount and microscopical picture is the same as in No. 15.

17. Length of experiment 35 days, received 6 doses of 0.171 gram each. Total 1.026 grams.

Microscopically shows congestion and edema. In both convoluted tubuli and Henle's loops precipitated albuminous network occurs. In all segments of the tubule there are a few small hyaline casts, some of which, especially those in the papilla, are impregnated by lime salts. Some of the epithelial cells of the Henle's loops and distal convoluted tubuli are detached from the basilar membrane; some show plasmorrhesis, others are without nuclei, and most of them are slightly vacuolated. Slight cloudy swelling, and fatty degenerative infiltration of the Henle's loops, distal convoluted and collecting tubuli.

18. Length of experiment 64 days, received 39 doses of 0.03637 grams each. Total 1.41843 grams.

Microscopically shows few casts and lime salt impregnations in papilla, vacuolated epithelial cells of the Henle's loops, distal convoluted and collecting tubuli—fatty degenerative infiltration—There are mitotic figures in epithelium of collecting tubuli.

19. Length of experiment 44 days, received 24 doses (14 of 0.06309, and 10 of 0.075945 gram each). Total 1.64271 grams.

Microscopically shows precipitated albuminous network in convoluted tubuli. A few hyaline casts, some of which are calcified, occur in distal convoluted tubuli and Henle's loops.

20. Length of experiment 54 days, received 27 doses of 0.075945 gram each. Total 2.050515 grams.

Exhibits congestion of glomeruli; precipitated albuminous network in proximal convoluted tubuli with slight parenchymatous degeneration of the epithelium; few hyaline and granular casts in the Henle's loops and distal convoluted tubuli. Lime salt deposits occur in four casts. Epithelium of Henle's loops, distal convoluted and collecting tubuli, especially papillary ducts, is finely vacuolated, indicating fatty degenerative infiltration. Here and there the nucleus of an epithelial cell stains very dark, and the protoplasm pinkish-blue, probably indicating proliferation.

21. Length of experiment 80 days, received 50 doses (39 of 0.03637) and 11 of 0.06309 gram each). Total 2.11242 grams.

Microscopically presents moderate congestion, and precipitated albuminous network in Bowman's capsule and proximal convoluted tubuli. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli are finely vacuolated, indicating fatty degenerative infiltration.

22. Length of experiment 80 days, received 50 doses (39 of 0.03637, and 11 of 0.06309 gram each). Total 2.11242 grams.

Presents networks of albumin in proximal convoluted tubuli. Epithelial cells of the Henle's loops and of the distal convoluted tubuli show distinct vacuolation, while those



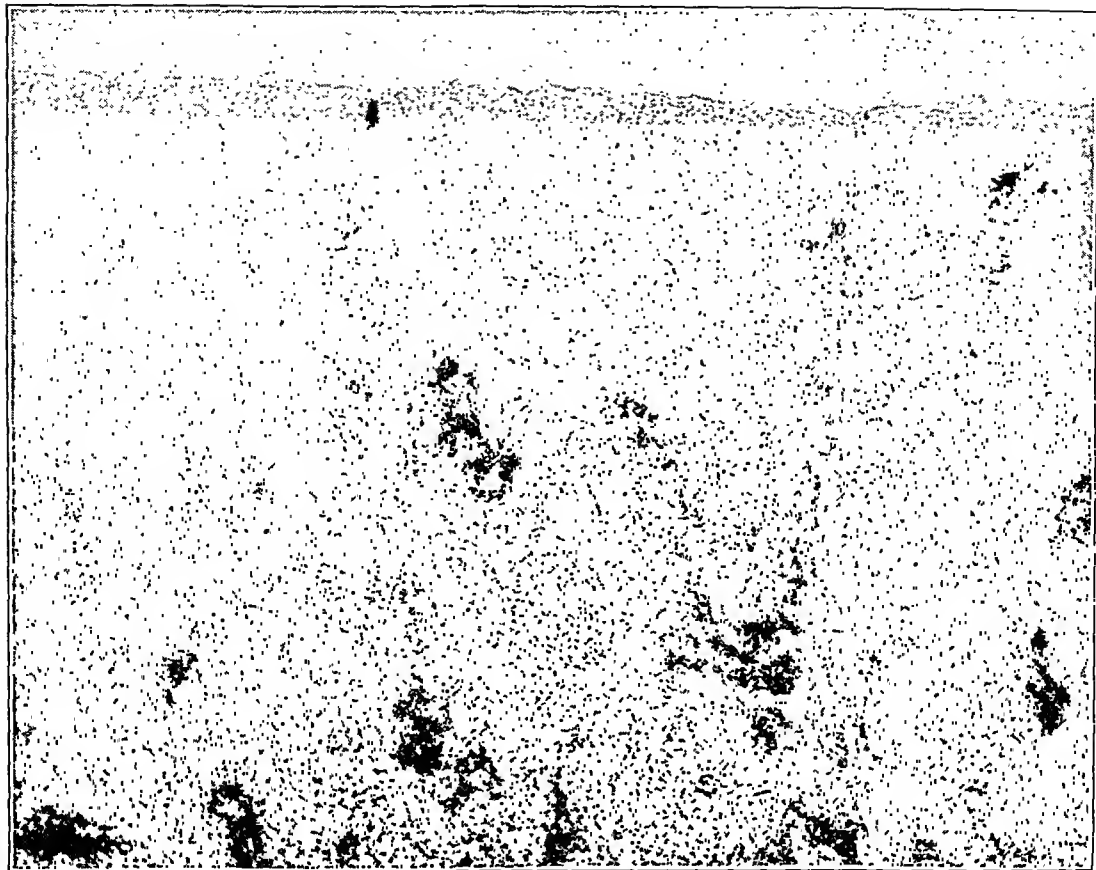


FIG. 2.—From Guinea-pig No. 20. Fatty degenerative infiltration of tubules in cortex. Scharlach-R stain.

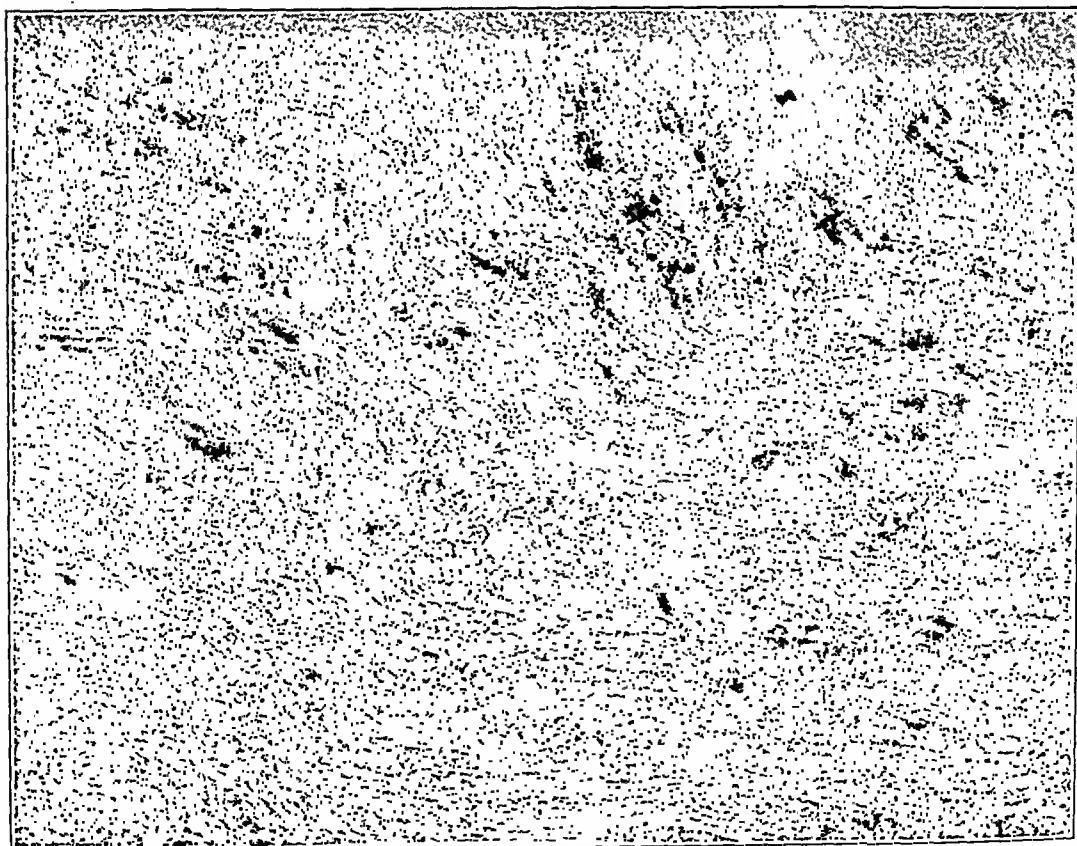


FIG. 3.—From same kidney as in Fig. 2. Scharlach-R stain. Fatty degenerative infiltration of epithelium of Henle's loops in cortical arch portion.

of the collecting tubuli are finely vacuolated—fatty degenerative infiltration.—Here and there are hyperchromatic nuclei and mitotic figures.

23. Length of experiment 85 days, received 51 doses (39 of 0.03637, and 12 of 0.06309 gram each). Total 2.17551 grams.

can see precipitated albuminous networks and a few casts. Epithelial cells of the tubules are finely granular, and those cells of Henle's loops and collecting tubules are slightly vacuolated. Fatty degenerative infiltration of the Henle's loops, distal convoluted and collecting tubules present. In

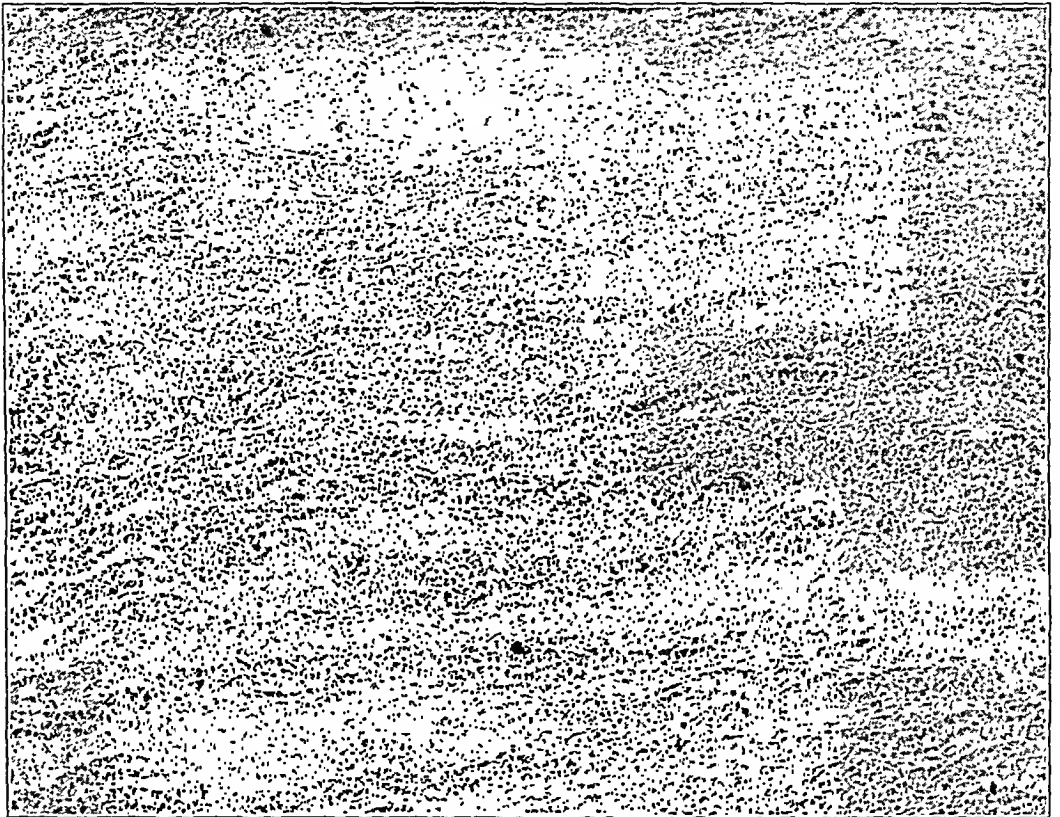


FIG. 4.—Medullary pyramid of same case. Scharlach-R stain. Fatty degenerative infiltration of tubular epithelium.

Presents precipitated albuminous network in the proximal convoluted tubuli, and few casts in the Henle's loops, most of which are infiltrated by lime salts. Fatty degenerative infiltration is indicated by the finely vacuolated appearance of the epithelial cells of the Henle's loops, distal convoluted and collecting tubuli. Occasionally hyperchromatic nuclei and mitotic figures are noted.

24. Length of experiment 54 days, received 16 doses of 0.171 gram each. Total 2.736 grams.

Microscopic picture presents marked congestion. In all segments of the tubules one

addition there is slight parenchymatous degeneration.

25. Length of experiment 81 days, received 36 doses (6 of 0.06309, 19 of 0.075945, and 11 of 0.0909 gram each). Total 2.82148 grams.

Microscopically shows moderate cloudy swelling of the proximal convoluted tubuli, few finely granular and hyaline casts in the convoluted and collecting tubuli, and Henle's loops, in some of which lime salt is deposited. Epithelial cells of the Henle's loops, distal convoluted and collecting tubuli

are finely vacuolated, indicating fatty degenerative infiltration, which is less marked in the thin part of the Henle's loops and smaller collecting tubuli, than in the ascending part of Henle's loops, distal convoluted tubuli and papillary ducts, where it is very marked. Mitotic figures are numerous, especially in proximal convoluted tubuli, evidencing regeneration of the epithelium,

but some of them, especially in collecting tubuli, are flattened out and pushed rather toward the lumen, the cytoplasm being clear, swollen. Fatty degenerative infiltration is shown in Henle's loops, distal convoluted and collecting tubuli. A few hyperchromatic nuclei and mitotic figures are also present.

27. Length of experiment 81 days, re-



FIG. 5.—Guinea-pig No. 25. Osmic-acid preparation. Fatty degenerative infiltration of epithelium of collecting tubules near papilla.

elial cells. Slight connective tissue proliferation in the cortex is noted.

26. Length of experiment 59 days, received 19 doses of 0.171 gram each. Total 3.249 grams.

Exhibits congestion; in Henle's loops and collecting tubuli are a few hyaline casts. In Henle's loops, distal convoluted and collecting tubules the epithelial cells are very clear, vacuolated or goblet-like. The nuclei of these cells usually appear normal,

received 21 doses of 0.171 gram each. Total 3.591 grams.

Shows congestion, edema and very few casts. In proximal and distal convoluted tubuli, and Bowman's capsules one sees precipitated albuminous networks. Cytoplasm of the Henle's loops, distal convoluted and collecting tubules is slightly vacuolated and finely granular. In all segments of the tubules, here and there, one observes the absence of nuclei; and also

hyperchromatic nuclei and mitotic figures. Nuclei of the distal convoluted tubules are situated rather toward the inner border of the cell. Cells of the collecting tubules are mostly detached from basilar membrane.

Diagnosis: Fatty degenerative infiltration of the Henle's loops, distal convoluted and collecting tubules. Regeneration of the

the collecting tubules. Protoplasm of the cells of distal convoluted tubules and Henle's loops is clear and more granular than normal. The inner margin of these cells is irregular, and in the lumina of such tubules one can see albuminous precipitate, sometimes in a network. The smaller collecting tubules show the same thing. In

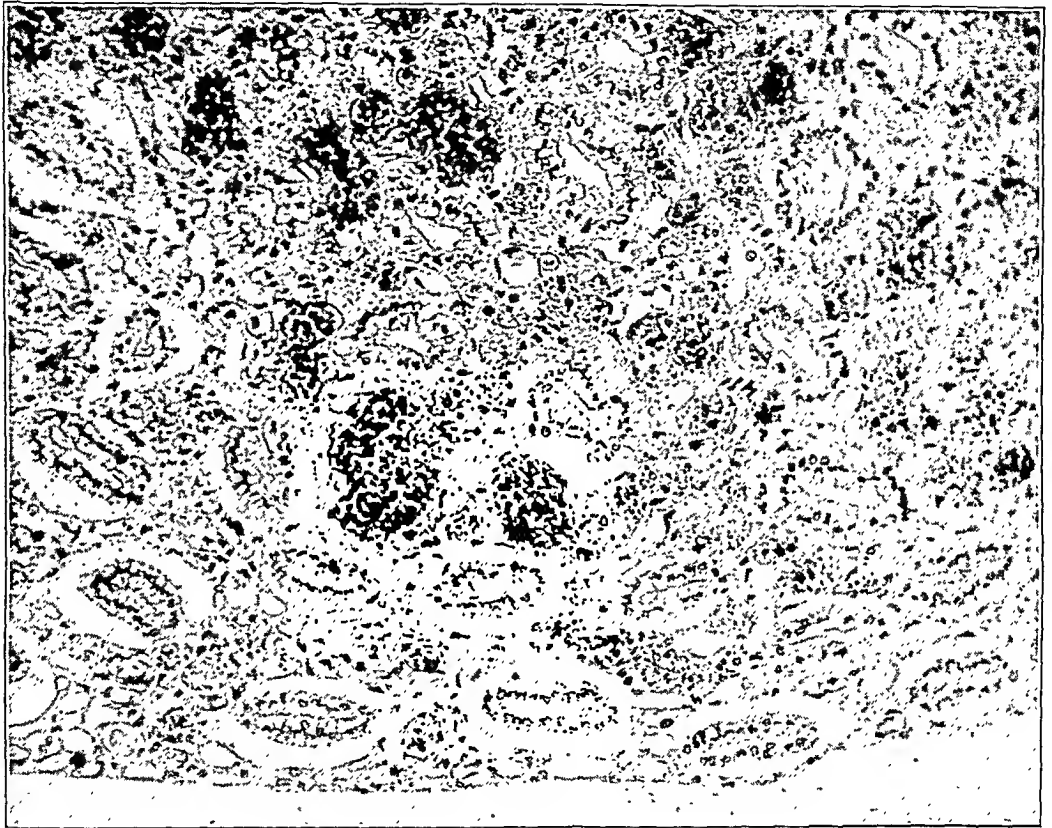


FIG. 6.—Guinea-pig No. 28. Hyaline casts and lime-salts in tubules of medullary pyramid, near papilla.

epithelial cells of all divisions of the tubules.

28. Length of experiment 57 days, received 22 doses of 0.171 gram each. Total 3.762 grams.

Shows little congestion, and in Henle's loops but few hyaline casts. In several of these casts (4 to 5) one can see small, dark-blue, rounded, structurless bodies, which correspond in their appearance to lime salt incrustations. In the papilla there are many such incrustated areas between

the larger ones, however, cells are detached from the basilar membrane; and the lumen is narrow or lacking, because due to the fact that the inner margins of the cells are either very close or approximate each other. Some of the nuclei of these cells are somewhat flattened out and lie rather toward the basilar part of the cells. Cytoplasm of these cells is clearer than normal, especially around the nuclei and basal part of the cells. There is a fatty degenerative infiltration of Henle's loops, distal convo-

luted and collecting tubules. Lime salt deposits are present in Henle's loops, collecting tubuli and in straight medullary rays. Parenchymatous degeneration in proximal convoluted tubuli is noted.

29. Length of experiment 93 days, received 53 doses (20 of 0.06309, 24 of 0.075945, and 9 of 0.0909 gram each). Total 3.90266 grams.

Microscopically shows a moderate degree of cloudy swelling in proximal convoluted tubuli and precipitated albumin here. In Henle's loops, distal convoluted, collecting tubuli and papillary ducts the epithelial cells are finely and coarsely vacuolated indicating fatty degenerative infiltration. There are very few casts. In all portions of the tubule one can see single desquamated epithelial cells of the proximal convoluted tubule epithelial type. Mitotic figures and regenerated epithelium, especially in the proximal convoluted tubule, are readily demonstrable. In the fatty tissue of one or two of the interlobular septa there is slight polymorphonuclear infiltration.

30. Length of experiment 95 days, received 55 doses (20 of 0.06309, 24 of 0.075945, and 11 of 0.0909 gram each). Total 4.0844 grams.

Microscopically presents parenchymatous degeneration and precipitated albumin in convoluted tubuli, finely granular and hyaline casts mostly in the Henle's loops located in the papilla, few of these casts containing lime salt. In collecting tubuli and papillary ducts may be seen clumps or casts of desquamated epithelial cells. Fatty degenerative infiltration is quite marked in the usual parts of the tubule.

31. Length of experiment, total amount of lead and microscopical picture are the same as in No. 30.

32. Length of experiment 161 days, received 98 doses (12 of 0.03306, 41 of 0.03637, 38 of 0.06309, and 7 of 0.075945 gram each). Total 4.816825 grams.

Microscopically presents dilated Bowman's capsules and proximal convoluted tubules filled with precipitated albuminous network, and few casts in the Henle's loops. Epithelial cells of the Henle's loops,

distal convoluted tubuli and in lesser degree collecting tubuli show fatty degenerative infiltration. Albuminous precipitate in capsular space would indicate also the lesion of the capsular epithelium. In the Henle's loops and collecting tubuli are several deposits of lime salt.

33. Length of experiment 180 days, received 109 doses (40 of 0.03637, 38 of 0.06309, 20 of 0.075945, and 11 of 0.0909 gram each). Total 6.37111 gram.

The pathological picture shows less fatty degenerative infiltration, but more hyaline casts than that of the No. 32, and several foci of small round cells. The important thing in this and the following three animals in the presence of small foci of very dark fibroblastic nuclei in the cortical zone, indicating beginning of secondary interstitial nephritis.

34. Length of experiment 180 days, received 113 doses (40 of 0.03637, 39 of 0.06309, 23 of 0.075945, and 11 of 0.0909 gram each). Total 6.662035 grams.

Pathological picture is similar to No. 33, but with more casts, lime salt in convoluted tubuli, and epithelial regeneration in the proximal convoluted tubuli. Very early connective tissue proliferation in the cortex.

35. Same as No. 34.

36. Length of experiment 202 days, received 130 doses (12 of 0.03306, 44 of 0.03637, 39 of 0.06309, 24 of 0.075945, and 11 of 0.0909 gram each). Total 7.28018 grams.

Grossly shows uniformly finely granular surface.

Microscopically presents cloudy swelling of the epithelium of the proximal convoluted tubuli with precipitated albumin and few casts, which are present also in the Henle's loops. Fatty degenerative infiltration is not marked. Characteristic for this section is the presence of the cystic dilated tubules in the cortical zone; these cysts are lined by cubical or slightly flattened epithelium and contain hyaline casts or precipitated albumin. A further characteristic feature is the proliferation of the interstitial connective tissue beginning at

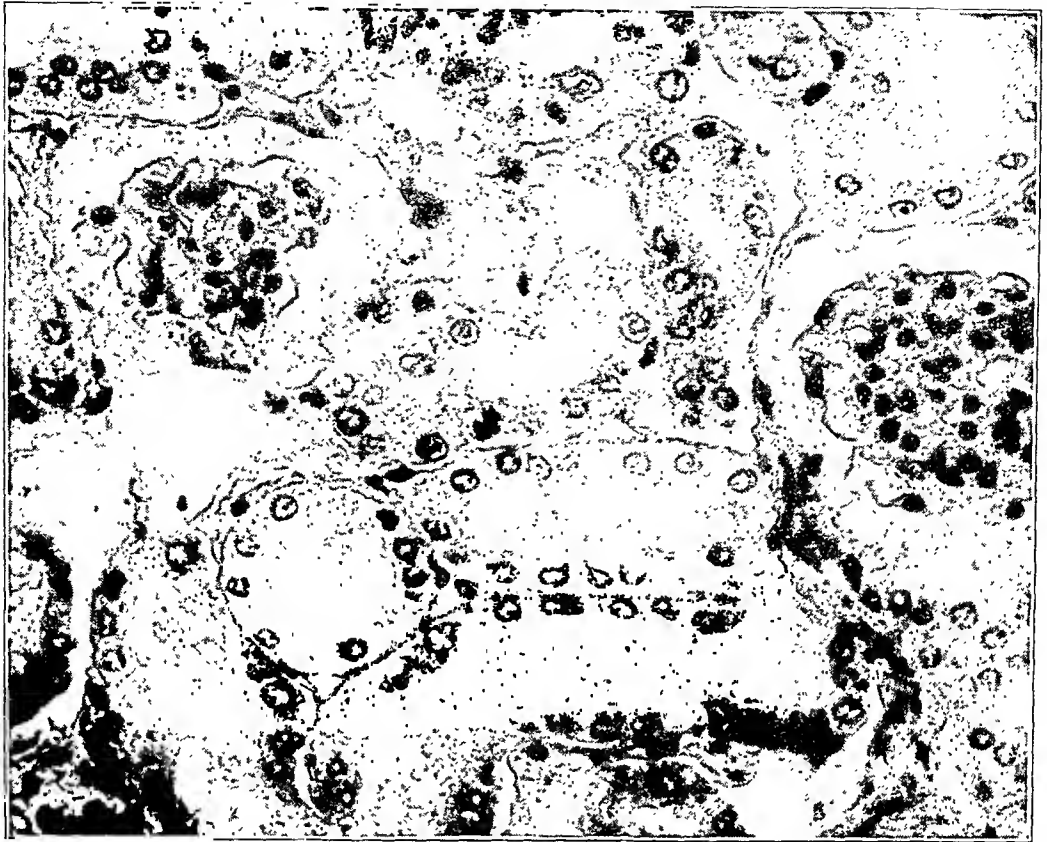


FIG. 7.—Guinea-pig No. 32. Glomerular and tubular changes.

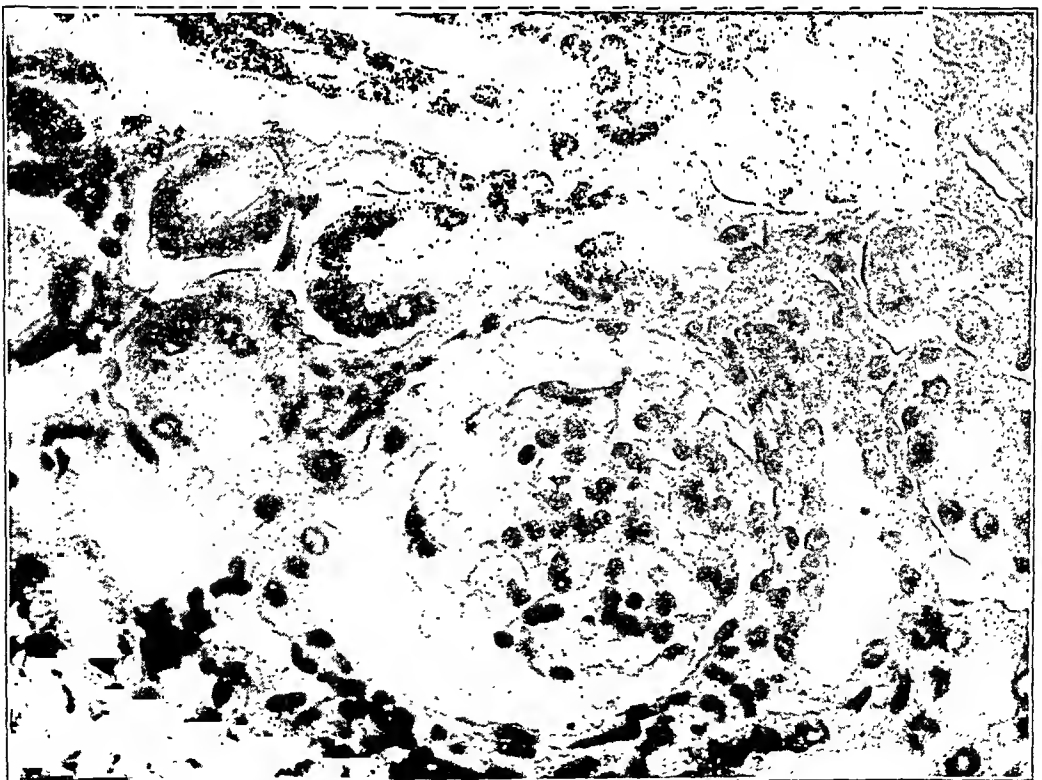


FIG. 8.—Guinea-pig No. 32. Higher power of glomerular and tubular lesions.



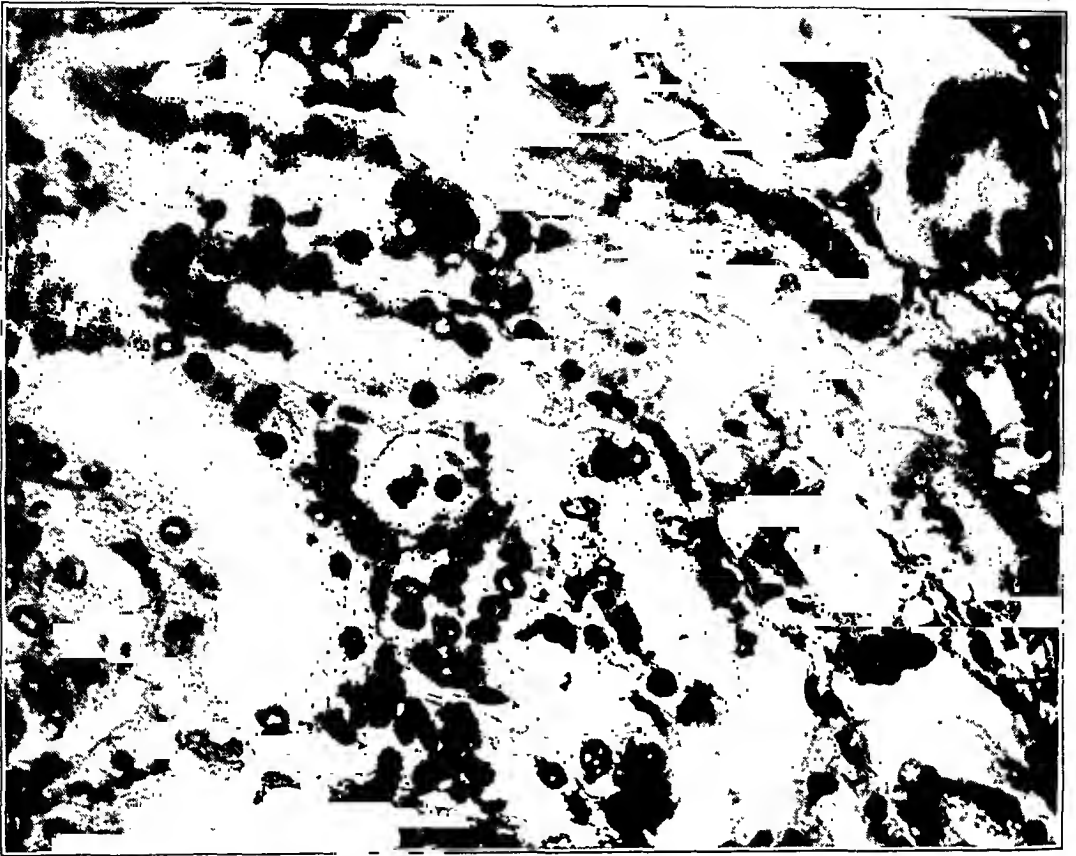


FIG. 9.—Guinea-pig No. 32. Tubular lesions.

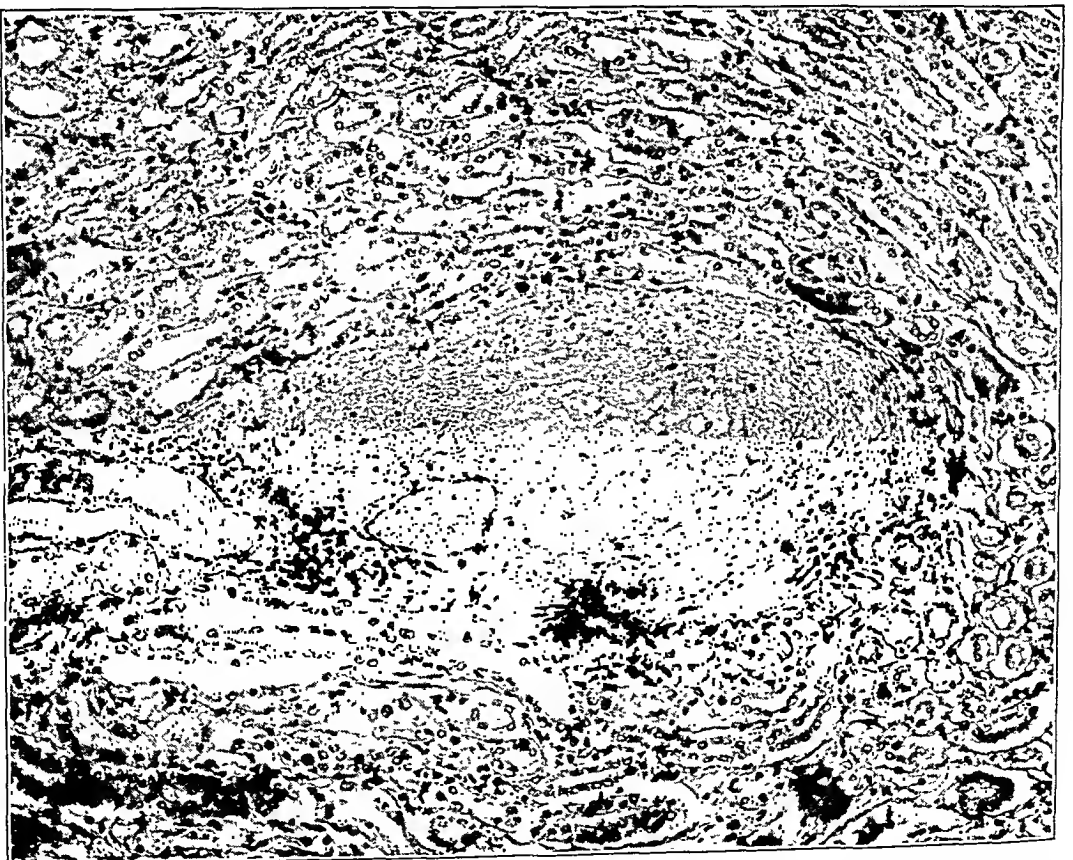


FIG. 10.—Small anemic infarct, with slight inflammatory reaction about it. Guinea pig No. 32.



FIG. 11.—Guinea-pig No. 33. Hyaline casts and hyaline thrombi in papilla.

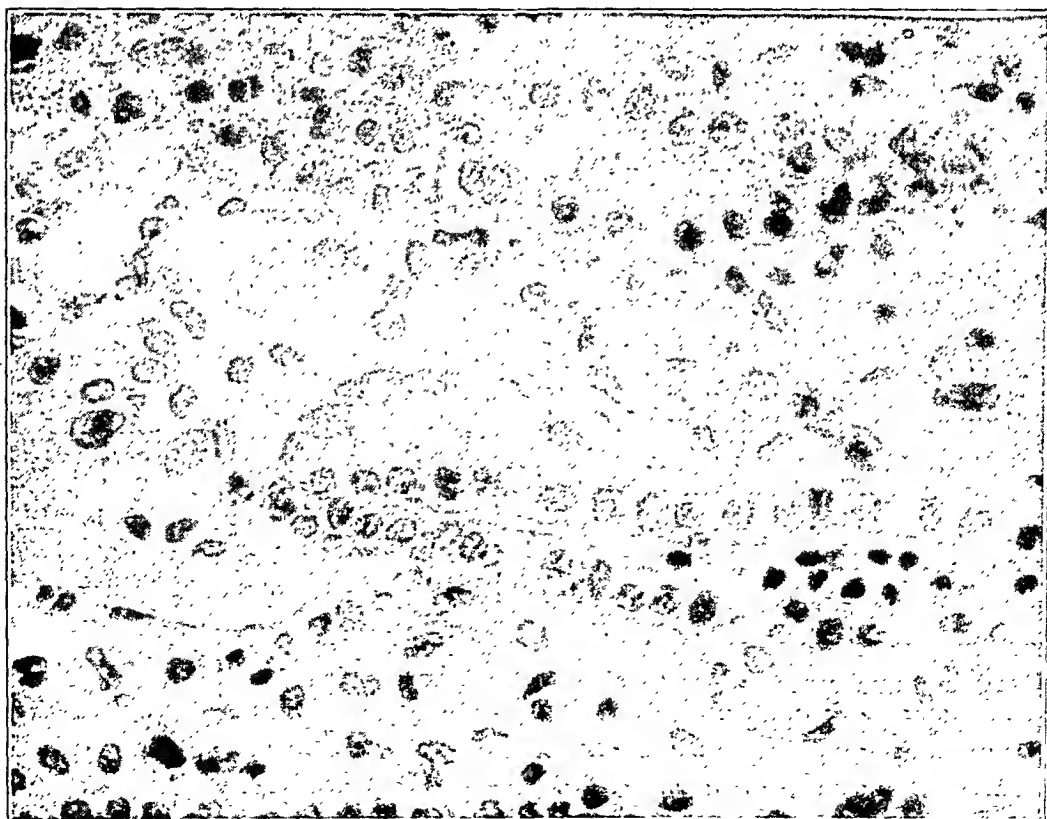


FIG. 12.—Higher power view of preceding.



the surface and extending deeper into the cortex.

### GENERAL DISCUSSION

It will be seen from the foregoing brief descriptions of the pathologic-histological findings in the kidneys of guinea pigs dying at varying experimental time and variable total dosages of lead, that the kidney lesions are mostly those of the initial stage, confined to epithelial damage, both in the renal tubules and Malpighian bodies. There are in the last four instances slight inflammatory changes in the kidneys, but in all others only those of circulatory and degenerative nature. The circulatory changes are expressed in the quite marked congestion, both active and passive, of the renal vessels and capillaries. This congestion is characteristic in most of these experimental animals with one or two exceptions. In agreement with Coen E. and e d'Ajutola, G. the glomeruli were usually found moderately or greatly congested. In several cases there was also edema and hydrops of the kidney structures. The most adequate explanation for this congestion seems to be the chemical irritation and altered metabolism of the kidney cells caused by poison, which irritation and change in metabolism causes a larger inflow of blood. An explanation on any other basis is difficult, because, according to Heubel (46), Rosenstein (47) and Siccardi (48), lead produces vasoconstriction and anaemia. Edema is simply the consequence of hyperemia, and hydrops in some cases is due to change in metabolism of the cells.

Although Legge and Goadby so strongly emphasize in their descrip-

tions and illustrations interstitial hemorrhages in the kidneys of lead poisoning both in animals and in man, it does not seem convincing to us, since in our series we have frequently seen identical pictures in the lead kidneys, but these we find are only congestion, and not hemorrhage. They state that "the venules rather than the arterioles appear to be the preliminary site of destruction." From their descriptions and plates it would appear that they did not always find the delicate venule walls intact. This does not necessarily mean, however, that such defects are pathological; they may very readily have been artefact due to contraction or stretching of the sections during the technical preparation.

The next characteristic change is the slight parenchymatous degeneration of the tubular and glomerulocapsular epithelium, particularly in that of the proximal convoluted tubules. In several cases in the capsular spaces and frequently in proximal convoluted tubules and even lower down there were present networks of precipitated albumin. However, in such early experiments albuminuria was not marked, corresponding to the findings of Oliver, Giglioli, and others, who in most of the cases found transient, or temporary albuminuria, and to the findings of constant albuminuria in human cases of chronic lead poisoning by Bright, Tanquerel des Planches, Lublinski, Von Leyden, Page, Castex, and Widai.

There were few hyaline and even a smaller number of granular casts, most numerous in the Henle's loops and collecting tubuli, but also occa-

sionally found in the convoluted tubulit. In several kidneys we have seen slight epithelial cell dequamation, and in three of these even epithelial casts could be seen in the collecting tubuli and papillary ducts. Proof that the thin parts of Henle's loops in the guinea pig kidney extend even into the papilla is offered by the finding of tubules in this location whose epithelial lining is that of this part of Henle's loop and, furthermore, by the presence of small and thin hyaline casts and lime salt deposits within the lumina of such tubules.

Attention is again called to the practically constant presence of lime salt deposits in the kidneys examined. As is generally known, the lime salt is deposited in areas of necrosis. Such is the case here also. These impregnations, it was found, begin primarily in the casts, and later, as they increase, lime spreads centrifugally into the adjoining epithelial cells and also the interstitial tissue. According to the distribution of the casts, the lime salt impregnations were most frequently found in the medullary pyramids in the papilla and near it, originating from the casts in Henle's loops and collecting tubuli and spreading toward the outside of the tubules. The lime salts were found in several instances in distal convoluted tubule casts also. In several instances, where the lime salts were in only small quantities, only a few granules, it was clearly demonstrable that the impregnation begins in the casts. This finding of lime salt deposits is in accordance with that of the authors mentioned in the discussion of the

literature, particularly of Charcot, who found the lime salts in the thin parts of Henle's tubuli, and with those of Beer, E., who says:—"deposits in the connective tissues were extremely rare and adjacent to involved tubuli." Beer also noted the deposits in the papilla. In my preparations the lime salt was found to be calcium carbonate, since, upon application of sulphuric acid to sections containing the deposits, there developed gas bubbles due to formation of carbonic acid gas ( $\text{CO}_2$ ). The lime salt deposits found were better brought out in the Best's carmin preparations than in the hematoxylin-eosin sections.

The fourth characteristic of the early lesions of the renal tissue due to lead poisoning is fatty degenerative infiltration. This degeneration was not found in all the segments of the glomerulo-tubular epithelium. It is best developed in the epithelium of the ascending part of the Henle's loops, distal convoluted tubules and in the papillary ducts, and only in lesser degree in the collecting tubuli and thin parts of the Henle's loops. In no instance did the epithelium of Bowman's capsule and proximal convoluted tubuli show this lesion. The fat droplets are situated mostly in the basal part of the cells. In the last four instances showing the beginning interstitial proliferation the fatty degenerative infiltration was very slight, which is important in regard to the beginning of the inflammatory process. In order to determine whether or not fatty degenerative infiltration occurs in normal guinea pig kidney, four healthy animals were killed and their kidneys examined for fat. To elimi-

nate possible error due to excessive adiposity, animals of different body weights (468 and 496 to 610 and 740 grams respectively) were chosen. The kidneys of these animals were fixed and stained in exactly the same manner as those of the lead animals. No fat was found in these controls. Therefore the statement of some authors that the kidneys of normal, healthy guinea pigs show fatty degenerative infiltration is unconfirmed. In my opinion the finding of fatty degenerative infiltration in the kidneys of supposedly normal experimental animals may be due to the fact that they are latently ill because of improper diet or hygienic care. This demonstration of fatty degenerative infiltration in the kidney tubuli confirms the reports of Oliver, Kobert, Delafield and Prudden—F. C. Wood, and Anino. Whether or not these early degenerative lesions are due to direct action of lead upon the renal epithelium or are the result of anemia produced by this poison is uncertain. It seems possible that the deleterious results may be due both to the direct action of lead and to the anemia caused by it. However, the negative finding of fatty degenerative infiltration in the kidneys of animals, dying shortly after beginning of the experiments, would indicate that the fatty degenerative infiltration probably is not due to the direct action of the lead, at least not in those in which only a small amount is ingested, but rather to the anemia produced by lead, and thus to indirect action of the lead.

All these findings: circulatory changes, degenerative parenchymatous

and fatty lesions, hyaline and granular casts and lime deposits are proof, that the earliest renal lesions, due to lead carbonate poisoning, are of a degenerative nature.

While all these lesions are of retrogressive character, there are instances of proliferative and regenerative nature also; since in several of kidneys examined very hyperchromatic nuclei, and frequently distinct mitotic figures of the epithelial cells were seen. These show rather bluish-pink protoplasm, oval shaped cells with the long axis usually in the circular or longitudinal direction of tubule, not, as normally, in the radial direction. This indicates regeneration of the damaged epithelium of the tubules. This finding confirms the similar reports of Charcot et Gombault, Ophüls, Coen E., e d'Ajutola, and Page.

Glycogen infiltration of the kidneys was not present in any of the experimental animals.

Likewise, there were no microscopic vascular lesions such as degeneration of the media or proliferation of intima in the kidneys of any of my animals, which is in disagreement with the opinion of the second group of authors, who believe that the vascular lesions are primary in the lead kidney. According to this negative finding of vascular lesions for the first six to seven months of the experimental time, during which epithelial lesions are demonstrable, the primary renal lesion due to lead poisoning is parenchymatous degeneration and fatty degenerative infiltration of the epithelium, followed by secondary

interstitial nephritis. If there are vascular lesions due to lead poisoning alone, as the students of human material report, these are only secondary and in very advanced stages of the lead kidney.

The beginning of secondary interstitial nephritis was found only in the last four animals i. e. in those which lived longest (6 to 7 months) and which had the largest amount of lead carbonate (6.37 to 7.28 grams). This was not very marked, but only in the first stage of interstitial proliferation with young dark nucleated fibroblasts, rich in cells, and without old scars or connective tissue hyalinization. This was marked only in the oldest animal in the outer zone of the cortical substance.

Although the number of animals living more than six months is too small from which to draw definite conclusions regarding the changes characteristic of chronic lead nephritis, so far as my results go they support the findings of Ophüls, who states that the character of the kidney lesions in experimental animals given lead carbonate less than six months is parenchymatous degeneration, necrosis, desquamation, and now and then regenerative evidence, characterized clinically by few casts and very slight or no albuminuria, and that the interstitial nephritis begins to develop secondarily, and only in those animals, which are experimented upon six months or more.

If we judge by the pathological lesions caused by different total doses of lead and various experimental time in several guinea pigs, we are forced to the conclusion that the changes in

the lead kidneys are not dependent exclusively on the total amount of lead and experimental period. As we saw from the descriptions, the lesions and the degree of lesions are not absolutely the same in all of the animals, which received the same amount of lead for the same period; and on the other hand, there are similar lesions of the same or nearly the same degree in the animals, which received different amounts of poison for various experimental periods. Therefore, it must be noted that the kidney lesions in lead poisoning depend also upon an individual susceptibility, predisposition or resistance to the lead. This may be an inherited predisposition, susceptibility or resistance or it may be required in many ways.

#### CONCLUSION

On the basis of the foregoing results and from the discussion the following conclusions may be drawn:

1. That the earliest lesions in the guinea pig kidney due to lead carbonate poisoning are moderate parenchymatous degeneration and fatty degenerative infiltration of the renal epithelium, without any microscopical lesions of the blood vessels.

2. That these early renal epithelial lesions with resulting precipitated albumin, slight desquamation, moderate numbers of casts and lime salt deposits, providing that no other etiological factor can be found, are the only lesions up to six months duration of the experiments and when lead carbonate in amounts between 0.5 and six grams has been given. Both the time and amount of lead required to

bring on these changes is conditioned somewhat by individual variation in reaction of the experimental animals.

3. That after six months and when more than six grams of lead carbonate has been given there begins, first in the cortex, a slight proliferation of the interstitial connective tissue, which toward the end of the seventh

month and when the total amount of lead carbonate given is over seven grams, leads to secondary contracted kidney.

In conclusion the author wishes to express his gratitude and appreciation to Dr. Aldred Scott Warthin and Dr. Carl V. Weller, under whose direction and guidance the work was carried out.

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# Hookworm Disease Causing the Blood Picture of Primary Hemolytic Anemia in an Infant

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**I**N speaking of anemia in infancy Cabot (1) says there is apt to be (a) enlargement of the spleen, (b) leukocytosis, (c) high color index, with megalocytic blood picture, (d) erythroblasts, many of them megaloblasts, (e) abnormal leucocytes (myelocytes, stimulation forms), and that these findings make it so difficult in infancy to recognize the type of blood disease from the blood alone that the attempt should not be made—a view borne out in detail by the following case.

Case history: In October 1924, a twelve months old baby was referred to me by Dr. A. F. Thompson of Troy, N. C. The baby was very pale and weak, and had been vomiting about once a day for several months. The parents and other children seemed healthy. This baby was born at term and labor was normal. She had never been sick otherwise and was still almost exclusively breast fed. There was a history of having swallowed a small metal piece from a pocketbook at the age of five months, and at nine months the baby became yellow, pale and weak. The whites of the eyes were never yellow and the lemon-tint of the skin was not as pronounced as it had been at first. The

child was very fretful and at times felt hot. The parents attributed the sickness to the foreign body.

On examination the anterior fontanelle was found to be the size of a dime; skin very pale with strong lemon-yellow tinge, sclerae white; throat, heart, and lungs negative. Three incisor teeth were present and one coming through. Peripheral glands were not palpable. The spleen extended an inch below the costal margin and the lower edge of the liver was palpable at the costal margin. An X-Ray examination by Dr. J. Rush Shull failed to reveal any foreign body. The child was found to be running a continued temperature from 100 to 102. The feces were strongly positive for occult blood and crowded with hookworm eggs. Examination of the blood showed hemoglobin 47%, red cells 2,470,000 giving a color index of approximately 1; leucocytes 12,000, with polynuclears 56%, small mononuclears 41%, large mononuclears 2%, neutrophilic myelocytes 1%, eosinophils 0. The red cells showed moderate variation in size and shape with some polychromatophilia. There were 360 normoblasts and 120 megaloblasts per cu. mm.



Because of the very poor condition of the child transfusion seemed advisable and Dr. A. G. Brenizer gave 120 cc of blood into the longitudinal sinus.

Hookworm disease is the last thing I should have suspected as the cause of anemia in an unweaned twelve months baby who not only could not walk but would not leave its mother's arms at all, for Darling (2) points out that "infants under one year rarely or never harbor hookworms."

The picture of primary hemolytic anemia (except for hemolytic icterus) is rare in childhood and extremely rare in infancy, but as Lucas (3) points out more than half the reported cases were supposed to be due to intestinal parasites. The anemia of hookworm disease is almost invariably of the chlorotic type with low color index but as pointed out by Dock and Bass (4) a few cases occur in which the number of red cells are reduced as much as the hemoglobin, giving rise to a color index of 1 or above.

During the summer the older children had taken the baby into the back yard and holding her up had tried to teach her to walk, selecting soft

muddy ground to avoid hurting her feet.

As an intern in 1906, before much was known about hookworm in this country, I nearly killed a sixteen months old breast fed immigrant baby by starving it part of a day and giving thymol. The present patient, because of fever, anemia, and malnutrition, seemed too sick to stand much starving and purging. She was weaned and established on milk and oatmeal gruel before treatment was undertaken; then milk was withheld for a day before and after the giving of thymol, gr. 1, but during these two days oatmeal feedings were given at the regular intervals.

Dr. Thompson reports (1928) that after a number of treatments, covering a period of four months, all the hookworms were expelled, and the child has been normal ever since.

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# Evidence Concerning the Effect of Insulin On Carbohydrate Tolerance

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PREVIOUS to the discovery of insulin the treatment of diabetes mellitus consisted entirely of dietary measures. Various writers outlined methods of procedure which were calculated to maintain a sugar free urine and still keep the patient fairly well nourished. These experiments met with a variable degree of success, depending on the severity of the disease in the patients under their care.

The discovery of insulin changed the treatment of this malady as no treatment has been changed before. The early writings on insulin which appeared shortly after the completion of the experimental work which led to its discovery, give one the impression that the remedy was destined only to control diabetes in all stages, (1). These experimenters were not willing to forecast an increase in the carbohydrate tolerance as a result of its use. This same conservative attitude is held by many writers to-day, (2).

As was true before 1922, diet is to-day the most important part of the treatment of diabetes. No case will progress favorably unless the diet is carefully adjusted to the patient's needs, and after the diet has been devised for a given patient that patient

must be instructed in the proper preparation of the food and the calculation of the various amounts.

He should know why he is given a certain number of grains of carbohydrates, protein, and fat, and he should know how to properly calculate the amount of the various food substances. It has been my experience that the reliability of a patient, his ability to refrain from "cheating," depends to a great extent upon the character of the diet. If he can eat the same food that is served to others in the same family he will be better satisfied with his diet.

I have considered this matter in selecting a method of computing the diets given my patients. Dr. Orlando Petty (3) described such a method of diet calculation and it is his method that I have used. Patients using this diet are able to eat anything served in the average American home except pastry, pie, cake, candy, wheat bread, and other similar high starch foods. No extra cooking is required by the housewife in the diabetic family. This allows a more natural life and the tendency is towards honesty with himself and his physician.

The ratio between the protein, fat, and carbohydrate is so adjusted that there is no excess of anyone which

requires the addition to the diet of extra food materials such as olive oil, mayonnaise, cheese, cream in quantities greater than the usual person would enjoy. This is done by feeding the patient one gram of protein per kilogram of body weight, and sufficient fat and carbohydrate in ratio of 3 to 1 by weight, to make a total of 30 calories per kilogram. The ketogenic-antiketogenic ratio for diets calculated thusly is less than two and one quarter to one which leaves a safe margin, according to work done by Woodyatt (4).

Insulin has been used in cases placed on this diet, called by Petty an efficiency diet, when the carbohydrate tolerance of the individual was below the total glucose value of the diet. The patients are started on the diet and frequent blood sugar estimations are made. If the fasting blood sugar level falls to a level near normal, insulin is not used. If it fails to fall sufficiently or if it increases, insulin is used in sufficient amount to maintain the fasting blood sugar at a low level. This dosage is changed from time to time as the blood sugar permits. After the initial training period the cases are seen once a month for blood sugar estimations and the insulin dosage is adjusted accordingly. The insulin is divided into from one to four doses daily depending on the total amount to be given. It is injected just before mealtime, the fourth dose being given at midnight when necessary.

These patients are instructed to examine the urine weekly for sugar as an added precaution. However, I have discontinued relying on urinary

sugar tests as a means of governing the dosage of insulin because I have found several cases where the renal threshold was so high or so low that the Benedict test was of little value. Several of these cases showed symptoms of diabetes, polyuria, polydipsia, and pruritus with a sugar free urine and after a more careful examination a high blood sugar.

William Brace (2) has recently shown that there is no improvement in the carbohydrate tolerance in cases treated by insulin and the Newburgh high fat diet (5). This is quite contrary to my experience and to work done by McCallum, J. R. Williams and others (6) (7) and (8).

I therefore wish to report several cases from my series as further evidence in favor of the opinion expressed by McCallum.

Report A—Case No. 14352. A woman, age 54, entered the hospital in April 1925 suffering from polyuria, polydipsia, burning on urination, pruritis and restlessness. She was obese and had lost no weight recently. The urine was positive for sugar and the blood showed a sugar concentration of 0.40%. She weighed 201 pounds and was five feet, one and one-half inches tall. She was placed on a diet of 1800 calories, and required fifty units of insulin daily to keep the urine sugar free and the blood concentration below 0.20%. After two weeks she was discharged on 35 units daily with a blood sugar of 0.18% and no symptoms. Two weeks later the blood sugar had reduced to 0.16%, accordingly the insulin was cut to 25 units.

She continued to improve and the insulin was gradually reduced until the following May when the blood sugar remained at 0.12% with no insulin. She has had no insulin since and the sugar concentration has been between 0.09% and 0.11% at six examinations over a period of 18 months,

CHART "I" REPORT A

Date	Blood sugar	Insulin	Date	Blood sugar	Insulin
4-2-25	0.400%	40 units	5-27-25	0.138%	25 units
3	0.182	40	6-12-25	0.133	24
4	0.250	50	7-14-25	0.143	20
5	0.222	50	8-14-25	0.099	16
6	0.222	55	1-14-26	0.101	8
7	0.200	50	2-14-26	0.115	4
8	0.200	50	4-16-26	0.200	6
9	0.200	50	5-18-26	0.091	0
11	0.182	50	7-1-26	0.093	0
12	0.182	50	9-16-26	0.100	0
13	0.154	40	1-3-27	0.237	0
14	0.182	40	6-13-27	0.092	0
15	0.182	25			

with the exception of one test which was 0.23% at a time when she was suffering from a severe bronchitis. Subsequent tests showed a return to normal, the last test being 0.09%.

Report B—Case No. 14180. This patient entered the hospital in March 1925, aged 41, complaining of polyuria, polydipsia, pruritus, and neuritis for the past 20 years. The urine was negative for sugar, acetone and diacetic acid, the blood sugar was 0.25%. She was placed on a diet of protein 60 grams, fat 100 grams, and carbohydrates 50 grams, and after two weeks the blood sugar level was constant between 0.18% and 0.19% on 37 units of insulin daily. All symptoms had disappeared and the urine remained sugar free. The diet was increased gradually from 1340 to 1600 calories, and has been kept at that figure ever since. She remained the same until September, 1925, when the blood sugar increased to 0.31% due to a nasal infection. After this infection subsided it returned to its previous level. In April, 1926, the sugar content fell to 0.13% and the insulin was gradually stopped. Since ceasing the injections the blood level has been constant between 0.14% and 0.16%. She is symptom free and has remained on the same diet continuously, with no change in body weight.

Report C—Case No. 13871. Five years previous to admission this patient was ex-

amined for insurance and was told he had diabetes. Three months later he was placed on a diet by his family physician. He gradually grew worse until one year before admission he was sent to a State institution for diabetic treatment. He was sent home on a high fat diet of 2500 calories and 84 units of insulin daily. On admission, in September 1924, he complained of pains in feet made worse by walking and worse at night; weakness, some nausea after eating and palpitation. Weight 155½, height 5'11½", age 37. The urine contained acetone and diacetic acid, but no sugar. The blood sugar was 0.408%. The diet was reduced to 1980 calories, consisting of 70 grams protein, 160 grams fat, and 65 grams carbohydrate. Gradually the fasting blood sugar lowered and the urinary ketone bodies disappeared. Sixteen days after admission he was ready to work, and complained of no pain in his legs. The insulin dosage during this time varied from 75 to 80 units daily. In January, he was returned to the hospital because the sugar content of the blood had again increased to 0.333%. This was shown to be due to a rise of blood sugar during the night as he had been having a series of attacks of insulin shock during the day. After a week, the blood sugar content was constant at 0.112% on 77 units daily. He remained on this dosage until August, 1926, when he was reduced to 67 units resulting in a blood sugar level during the next six months below 0.167%.

In May, he again returned complaining of frequent attacks of insulin shock and after several days in the hospital was readjusted on 32 units of insulin daily with a blood sugar level below 0.10%. He has remained sugar free and free from insulin shock from then to the present time, on 32 units daily.

Report D.—Case No. 18055. A woman, aged 52, was admitted in September, 1926, to the surgical wards following an automobile accident in which she suffered a torn buttocks and perineum. After four days she became unconscious and cyanotic and on examination the urine was found to contain a large quantity of sugar, acetone and diacetic acid. The blood showed a sugar concentration of 0.4% and the alveolar air showed 15mm of CO<sub>2</sub> tension (Marriott). She was immediately placed on treatment for the impending coma. Fluids were administered subcutaneously. She was given digitalis tincture 15 minims every 3 hours and orange juice for its carbohydrate value.

She was given 150 units of insulin that day. That evening the sugar concentration

had fallen to 0.18%. The following day she received 110 units of insulin and the alveolar CO<sub>2</sub> was 30. On the morning of the third day of treatment the sugar concentration had increased to 0.44%, but during the day by giving 205 units it fell to 0.80%. She had regained consciousness and appeared quite normal. However, she required from 85 to 100 units daily for several days before the alveolar CO<sub>2</sub> increased to 35mm tension.

On the sixth day she received her first food other than the large quantities of orange juice given her up to that time. She was placed on a diet of 948 calories and this was gradually increased to 1800 during the next week. The alveolar CO<sub>2</sub> gradually increased to 45 in 11 days and the insulin treatment fell to none in 33 days (see chart).

The healing of the perineum was hindered by considerable infection but was complete in about two months and she was discharged from the hospital in 67 days on no insulin and 1800 calories, with a normal

CHART "2" REPORT D

Date	Blood Sugar	Insulin	Alveolar	Blood Urea	Urine	
			CO <sub>2</sub>		Sugar	Acetone
9-9-26	0.476%					
	0.334					
	0.182	150 units	15 mm	28 mg	pos	pos
10	0.334	110	30		pos	pos
11	0.444					
	0.400					
	0.080	205	30		pos	pos
12	0.286	80	30	44	pos	neg
13	0.308	100	30	40	pos	neg
14	0.250	85	35	20	pos	neg
15	0.200	70	30	26	pos	neg
16	0.143	60	30		pos	neg
18	0.160	60	40	12	neg	neg
20	0.133	50	45	12	neg	neg
24	0.129	35		11	neg	neg
29	0.105	20			neg	neg
10-1-26	0.133	15			neg	neg
12	0.052	0			neg	neg
11-15-26	0.141	0			neg	neg
1-29-27	0.100	0			neg	neg
4-5-27	0.084	0			neg	neg
8-13-27	0.095	0			neg	neg

blood concentration. Since discharge she has had three blood examinations running from 0.08% to 0.10% with no urinary sugar and no symptoms.

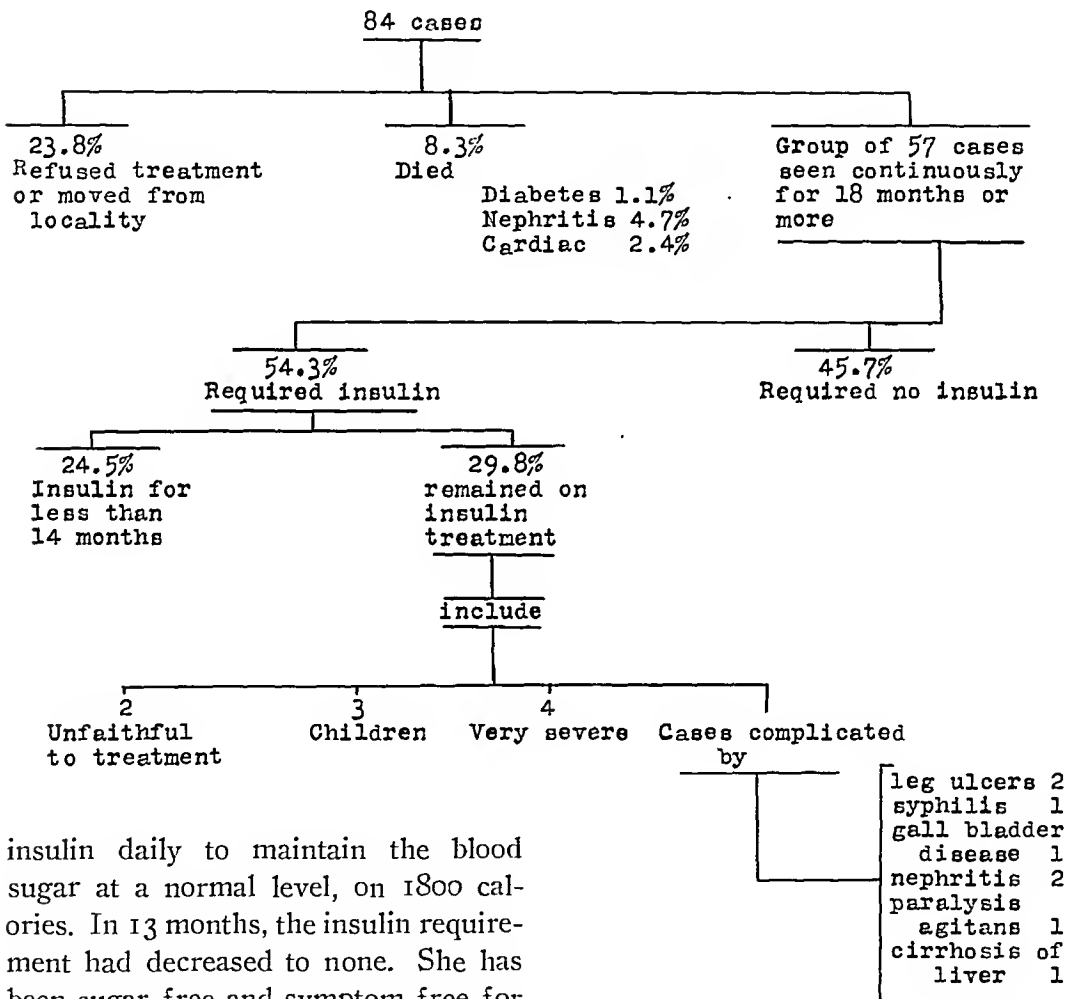
### DISCUSSION

*Report A.*—This presents the case of a woman who required 35 units of

require this amount for 13 months after which it was gradually decreased and she has maintained a normal blood sugar level on no insulin for the past year and a half.

*Report C.*—This man was growing worse on 84 units of insulin daily and

CHART #3



insulin daily to maintain the blood sugar at a normal level, on 1800 calories. In 13 months, the insulin requirement had decreased to none. She has been sugar free and symptom free for the past 18 months with a normal blood sugar and has remained on 1800 calories without loss of weight below the standard for her size and age.

*Report B.*—This case is very similar to the previous one. The patient was started at 37 units and continued to

a 2500 calorie high fat diet. He did not believe his symptoms were due to diabetes because his urine had repeatedly been negative but on examination he was found to have a very high renal threshold, in the region of 0.40% blood sugar. When this was

reduced by readjustment of the daily spacing of doses his symptoms rapidly left him. He required between 75 and 80 units daily for 24 months. Following this his requirement has gradually reduced to 32 units. He has maintained a normal blood sugar level on this dosage for the past 8 months.

*Report D.*—This woman was first seen in diabetic coma. She required considerable insulin during the first week (800 units) in order to reduce the acidosis. After recovery from the ketonemia the insulin requirement rapidly fell to nothing. The infection which resulted in the wound probably accounted for the amount of insulin required, but as the infection subsided the requirement fell and she has maintained a normal sugar level on no insulin for the past year.

Of a series of 57 cases which have been observed for longer than one year, 45.7% required no insulin, leaving 54.3% which required insulin as well as diet, to bring the blood sugar to a normal level.

Of the 54.3% requiring insulin,

24.5% were able to cease the injections in from 2 weeks to 14 months, the average time being 5.9 months.

There remains a group of 29.8% who have continuously required insulin. This group consists of irregular cases, two of them have been unfaithful with their treatment both dietary and insulin, three of them are under 20 years of age and consequently more severe, eight cases are complicated by ulcers, syphilis, gall bladder disease, nephritis, paralysis agitans, and cirrhosis of the liver. There are four other complicated cases which belong to this group. One of these has been reported in this article. They all require less insulin than when first seen, but are classed as "very severe" with a very low carbohydrate tolerance.

#### CONCLUSION

This resume is offered as additional evidence that in the absence of complications adult diabetics gradually improve their tolerance for carbohydrate, many of them to the extent that insulin is no longer required.

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# Addison's Disease in Association With Amyloidosis\*

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AMYLOIDOSIS is infrequently associated with the cause of Addison's disease. Autopsy findings in a number of cases at the University Hospital show that amyloid deposit in the adrenal glands occurs in a fairly large percentage of those subjects showing a generalized amyloidosis. The amount, however, is quite variable and in only two cases is it present in sufficient quantity to suspect the causation of symptoms and signs referable to adrenal insufficiency. On account of indefinite clinical evidence, combined with the fact that the subject is a negro, one of these cases cannot be diagnosed Addison's disease, although the cortex of both adrenals is almost completely replaced by amyloid. The one case for discussion, however, gives definite evidence of Addison's disease in association with marked amyloidosis of the adrenals.

It is agreed that the primary etiology of Addison's disease is varied, and that tuberculosis of the adrenals is undoubtedly the most common pathologic finding in association with this disease. Neoplasm, gumma formation, atrophy, hypoplasia, hemorrhage, infarction, and roentgenray necrosis are also occasionally found in connection with this condition. Autopsy findings on

patients dying in this hospital also show tuberculosis more frequently associated with Addison's disease than any other single condition. The review of 2550 autopsy cases reveals fourteen which can be classified under Addison's disease. The associated condition in these is:

Tuberculosis	7
Carcinoma metastases	4
Mycosis fungoides	1
Simple atrophy	1
Amyloidosis	1

Of these fourteen recorded, five are clinically diagnosed Addison's disease, and three others give a clinical diagnosis of (1) generalized tuberculosis with Addison's disease, (2) malignancy with Addison's disease, (3) chronic pulmonary tuberculosis with Addison's disease. The six remaining cases not clinically diagnosed give definite evidence of all six belonging to this group. On investigation, the clinical findings are found to be compatible with this diagnosis. Three additional cases give the typical pathological picture of Addison's disease, but there is no clinical evidence to substantiate the diagnosis.

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In regard to amyloidosis of the adrenals being a cause of Addison's disease, the literature shows only five other cases. All five showed marked amyloid deposits in the adrenals and have definite diagnostic proof of this disease being present. There are two additional reports by Riesman and Bauer which are somewhat doubtful; both show very marked amyloidosis of the adrenals, but neither gives a conclusive picture of adrenal insufficiency. Dickinson reports 118 cases of generalized amyloidosis, and of this number only nine show recognizable deposits in the adrenals; these cases show only a slight infiltration of the cortex with no apparent embarrassment to adrenal function.

A recent paper by Hunter discusses in detail the clinical and pathological findings in those cases previously reported. With reference to the adrenals, pathologic findings are fairly constant. The gross appearance shows the gland of normal or slightly increased size, increased firmness, yellow-white or grayish color, the cut surface giving a slight waxy appearance. Microscopic examination shows the amyloid in greater amounts in the cortex; the zona reticularis and fasciculata are most affected while the zona glomerulosa is only slightly involved. The medulla has only small deposits which are chiefly surrounding the blood vessels. All cases have a bilateral involvement of the adrenals.

#### CLINICAL REPORT

Mr. C. C., an American, carnival man, white, single, aged 45, entered the University Hospital November 2, 1927, complaining of weakness and

pain in the abdomen. The symptoms had begun gradually six months before with a feeling of fatigue. He developed loss of appetite, nervousness, insomnia, and a continual dull headache. The patient lost 25 pounds in these six months. There were no gastro-intestinal upsets with vomiting. Gradual weakness with a beginning swelling of the feet and ankles forced him to seek medical attention.

Past History—He had pneumonia in childhood. He gives history of marked sexual excess and has had gonorrhoea four or five times, also syphilis, which was inadequately treated. Patient has been a steady though moderate drinker for many years. Was married for 17 years, had no children. Has been separated for past five years.

Family History—Father died at 80 of unknown cause. Mother died at 80 of a stroke. Two sisters died of tuberculosis, one sister of influenza, and another died at birth. Otherwise the history is negative.

Physical Examination—Shows a chronically sick man, who lies in bed with no marked discomfort.

Pupils: Small and irregular, reacting sluggishly to light and to accommodation.

Dental Hygiene: Poor, and caries, pyorrhoea and gingivitis are marked.

Tongue: Heavily coated with no pigmentation present.

Mucous Membranes: Pale and show no pigment.

Ribs: Very prominent showing evidence of loss of weight.

Respirations: 18 per minute.

Upper Lungs: Clear, but there is a flatness at both bases with distant breath sounds, and a few scattered, fine rales over these areas.

Percussion shows the heart enlarged both to the right and left.

Cardiac Apex: Felt indistinctly 12 cms. to the left of the mid-sternal line. The sounds are distant. No murmurs are present.

Pulse: Rate is 80 per minute, and feels weak and small.

Blood Pressure: 80 systolic, 50 diastolic.

Abdomen: Rounded and tense, with evidence of fluid in the flanks. The liver edge is felt easily, but the liver is not definitely enlarged.

Extremities: Pitting edema of both ankles. Knee jerks are not obtained.

Skin: Shows no evidence of pigmentation or discoloration.

X-ray Findings: There is a small amount of fluid in both pleural cavities, cardiac enlargement, pulmonary congestion.

Laboratory Findings: Urinalysis shows a trace of albumin, many granular casts, no red blood cells. P.S.P. Test: Shows 45% in two hours.

Non-protein Nitrogen: 32.7 mg. per 100 cc.

Peripheral Blood: Shows 80% (Sahli), 3,800,000 R.B.C., 4,200 W.B.C. The differential count is not important.

Blood Wassermann: Reacts 4 plus.

Course in Hospital: Was steadily downward. Developed a definite pericardial effusion, with a suggestion of pulsus paradoxus present. Edema became generalized. Temperature was

always normal or subnormal up until two days before his death. Eleven days after his admission he developed a slight yellow discoloration of the skin over the lower face. This became more prominent, and deepened to a yellow-brown. At the time of death he showed a definite pigmentation of the lower face and upper neck. There also appeared to be increased pigmentation of both forearms. Blood pressure was 80/50 on three different occasions. The patient died fifteen days after admission.

#### PROTOCOL (abbreviated)

Mr. C. C., age 45, American, single, carnival man. Body is that of a white adult male of the typical asthenic type, with a light bony structure, and measures 161 cms. in length. Shows evidence of loss in weight in a fairly marked degree. Has long thin features. Neck is long and thin. Thorax is long and narrow. Intercostal angle is much less than a right angle. The intercostal spaces are depressed with the ribs prominent.

Skin is dry and inelastic. Over the greater portion of the body it is white, but there is a definitely pigmented area—yellow-brown in color—over the mid portion of the face. This begins on the bridge of the nose, and extends laterally and downward, over the lower face and upper portion of the neck. Both forearms and the dorsal surfaces of each hand show a definite yellow-brown pigmentation of the skin, which is contrasted with the white appearing and non-pigmented skin of the upper arms. Mucous membranes of mouth appear free of pigmentation grossly.

Left adrenal is slightly increased in size, and is surrounded by a moderate amount of fat. Cut section shows a strikingly hard and firm surface, which is wax-like in appearance. There is a definite patchy lipoidosis in the outer portion of the cortex.

Right Adrenal appears normal in size. Resembles the left in every other respect.

#### MICROSCOPIC EXAMINATION

Adrenals are almost completely replaced by amyloid, more marked in the medulla, and the inner portion of the cortex than at the periphery, where the glomerular zone and outer portion of the fascicular zone still show cells with excessive lipoidosis. Numerous syphilitic infiltrations are present in portions of the medulla. The large central vein is almost completely replaced by amyloid.

Semi-lunar Ganglia show marked deposits of amyloid in the ganglia and nerve trunks.

Pathological diagnosis is generalized amyloidosis of peculiar distribution, involving particularly the thyroid, pars intermedia of the hypophysis, heart and sympathetic nervous system, lungs, spleen, adrenals, pancreas, retroperitoneal vessels and the larger vessels of the hepatic trinity. Addison's disease. Old fibroid tuberculosis of lungs. Old syphilis. Syphilitic aortitis. Gumma of myocardium. Marked syphilitic pancreatitis, adrenalitis. Atrophy, chronic passive congestion and marked lipoidosis of all organs, particularly of the heart and kidneys. Myocardial failure. Hypertrophy and dilatation of both right and left ventricles. Relative tricuspid and pulmonary

insufficiency. Thrombus of right auricular appendage. Hydropericardium. Hydrothorax. Ascites. Edema of the glottis. Asthenic constitution.

#### COMMENT

The clinical diagnosis does not include Addison's disease, but the symptoms and signs are quite typical of this condition. The findings of particular interest are: complaints of increasing weakness, steady loss of weight, persistent constipation, abdominal pain, and anorexia. He showed a definite pigmentation of the skin, hypotension, sub-normal temperature, a comparatively slow pulse, and a fairly marked anaemia. In a recent article by Rowntree, who has observed a large number of cases clinically, it is shown that the most frequent symptoms present are asthenia, pigmentation, loss of weight, constipation, vomiting, nausea, anorexia, and pain in the abdomen. Hypotension is present practically in every case, and is not infrequently accompanied by a sub-normal temperature, and anemia. Undoubtedly the three essential factors which should be present to make a definite diagnosis are: (1) asthenia, (2) pigmentation of the skin, (3) hypotension.

Pigmentation of the skin became apparent in this case only shortly before death. Records show a marked variation in the time of appearance. The report by Hunter states that pigmentation was first noted only three days before death. Rowntree observed that it appeared at varying stages of the disease, sometimes only present for a few days, in others for months, and in a few instances it was present for years. He also gives mention to the

variation in intensity of the pigmentation present, which may occur at different periods of the disease. Warthin reports a case of Addison's disease where pigmentation was definitely present over a period of more than four years.

Pathological findings in relation to the probable cause of this disease are very interesting. According to the views held by Wiesel the development of this disease is definitely dependent upon lesions of the chromaffin system, whether in the medulla of the adrenal or elsewhere in the body. Von Hanse-  
mann and Karakascheff disagree with this view and state cases of definite Addison's disease with only the cortex of the adrenals being involved, the medulla entirely escaping. Fahr and Reiche, and more recently McCutcheon also favor the association of Addison's disease to damaged cortex. McCutcheon holds that the rarity with which amyloid disease produces the Addison syndrome is not dependent on the preservation of the adrenal medulla, but rather on the fact that the cortex is not completely destroyed by the infiltration, many cell groups escaping. All five cases reported of Addison's disease caused by amyloid show a marked involvement of the inner two zones of the cortex with comparatively little damage to the medulla. This evidence definitely favors the presumption that damaged cortex and Addison's syndrome are directly connected. On account of the marked involvement of both cortex and medulla, the case now being reported does not favor either theory. It is proof, however, that amyloidosis of the adrenals, when present in sufficient quantity, will give the typical picture of Addison's disease.

In summary we have: (1) a case of Addison's disease with marked amyloid deposits in the adrenals, sympathetic semi-lunar ganglia, and nerve trunks, (2) amyloidosis is generalized, and associated with a combined tuberculous and syphilitic infection.

NOTE: Another case recently coming to autopsy warrants mention on account of amyloid deposits found in the adrenals with total absence of a similar deposit in any other organ of the body.

The clinical aspect given briefly is: A man of 59 entered the hospital complaining of weakness which had begun gradually five years before. The clinical picture and blood findings were compatible with the diagnosis of pernicious anemia. Satisfactory response was obtained by the administration of liver extract over a short period. Cardiac damage was very marked and shortly after admission he developed broncho-pneumonia which finally caused his death.

The findings at autopsy show the adrenals to be hypoplastic with a slight lipoidosis of the cortex. Otherwise the gross appearance denotes nothing abnormal. Microscopic examination reveals a marked atrophy in the medulla of both adrenals with many areas of amyloid deposit present. There is also moderately marked lipoidosis of the outer portion of the cortex.

The paramount points of the pathological diagnosis are: Primary adenocarcinoma of the prostate. Severe purulent prostatitis. Posterior urethritis and cystitis. Metastatic lobular purulent pneumonia with acute purulent broncho-pneumonia on an older organizing lobular pneumonia. Severe secondary non-hemolytic anemia. Atrophy of adrenals with amyloidosis.

The amyloid deposit in the adrenals shows moderately well with the usual hematoxylin-eosin stain. This is shown definitely to be amyloid by the special Van Gieson stain. Though this subject manifests no evidence of adrenal insufficiency, it is of academic interest to note the occurrence of amyloid in both adrenals while those organs more prone to be affected have escaped.



FIG. 1.—Extensive amyloidosis of adrenal, with Addison's syndrome. Generalized amyloidosis.



FIG. 2.—Other adrenal of same case. Both adrenals nearly wholly replaced by amyloid.

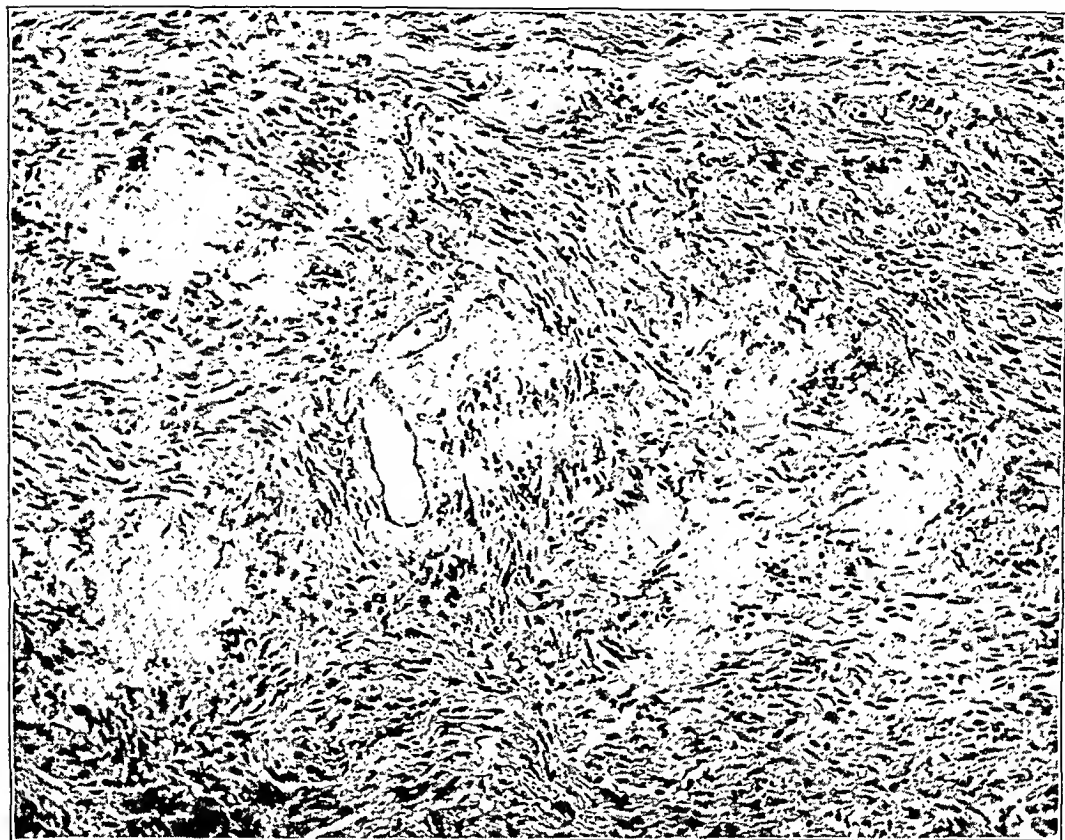


FIG. 3.—Amyloidosis of solar plexus. From same case as preceding.



FIG. 4.—Area of amyloid in adrenal, around adrenal veins. Gave typical metachromatic staining reactions for amyloid. No amyloid found in other organ or tissue.

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## Editorial

### THE CONSTITUTIONAL FACTOR IN PEPTIC ULCER

The experimental attack upon the etiological problem of gastric ulcer has led to no conclusive results. Experimentally-produced ulcers, no matter by what form of local injury they have been developed, have all differed essentially from human ulcers in that they usually quickly heal, while in man gastric ulcer is characterized essentially by its markedly chronic course. Further, the effects of local trauma to the gastric mucosa vary greatly in different animals; no one of the causes adduced for ulcer production is constant in its action, and, so far as man is concerned, no etiological entity can be shown to exist in the form of extrinsic factors. We are confronted here by the same etiological problem as that of gastric cancer. Inasmuch as the general problem of cancer etiology has been cleared up by the animal experimental investigations of the last fifteen years which have conclusively demonstrated that intrinsic factors of constitution and organ-predisposition determine the origin and site of cancers, it is but natural that we should seek a similar explanation for ulcer of the stomach. If such intrinsic factors exist they must show themselves in heredity. It is necessary, therefore, in the first place to determine if there is any evidence of heredity in the case of gastric ulcer, and for this evidence we must turn to available

statistics of gastric ulcer. Such evidence is singularly lacking in the textbook articles on gastric ulcer. Neither the first edition of Osler's textbook or the present year's edition of Osler's *Modern Medicine* mention the familial occurrence of gastric ulcer. It was not until the birth of the new medical philosophy of the *constitution* in the early years of this century that students of gastric ulcer began to take note of its multiple incidence in certain families. The first important observation upon this subject was that of Huber in 1907, who reported eleven cases of his own observation and nineteen seen by Bernhard. These observers were fully convinced of the fact of a hereditary predisposition to gastric ulcer; Huber thought it was present in 15 per cent of all cases, while Bernhard concluded that a hereditary predisposition was present in a third of his cases. In 1910 Czernecki reported a family in which a mother and two children all had gastric disease, all three of them with bleeding gastric ulcers, while two other children had hyperchlorhydria and gastric neuroses; all members of this family were of asthenic habitus and neuropathic. Westphal in 1914 collected fourteen cases, one-fourth of all his ulcer cases, in which there was multiple familial incidence of ulcer and gastric neuroses, with a high percentage of cases of carcinoma of the stomach. Plitek and Kodon also reported



observations on "ulcer families," noting the association of asthenic and neuropathic constitutions. R. Schmidt in 1916 observed in his clinic that the children of ulcer patients showed a multiple incidence of gastric ulcer. In the decade 1910-1920 the rapid development of constitution-pathology led to many observations on familial organ-predisposition, and a number of these were concerned with stomach conditions, gastric ulcer, hyperacidity, gastric neuroses, etc. (J. Bauer, Jung and others.)

In 1918 Ernst Spiegel made a special study of the question as to whether gastric disease was of more frequent occurrence in the families of ulcer patients than in the families of normal individuals. What is inherited is, of course, not gastric ulcer itself, but a pathological predisposition, and this may show itself in the form of ulcer, cancer, neurosis, or some other type of lowered gastric value. Spiegel studied the family history of 121 ulcer patients and 200 normal stomach individuals. He found that 74 (61.1 per cent) of the families of ulcer patients showed other cases of gastro-intestinal disease, while in the families of normal stomach individuals only 31 (15.5 per cent) showed other cases of gastric disease. In other words gastro-intestinal disease was nearly four times as frequent in the families of the ulcer patients as in the families of the non-ulcer cases. This study was carried out with the greatest care as regards intelligence of the patient, physiological consideration, age, state of nutrition, personal habits, etc. Of the families of ulcer patients 32 (26.4 per

cent) showed ulcer symptoms, 18 (14.8 per cent) had carcinoma of the stomach, 4 (3.3 per cent) carcinoma of other portions of the gastro-intestinal tract, while 20 (16.5 per cent) had illy defined gastric disturbances. Comparing this with the families of non-ulcer cases ulcer in 11 (5.5 per cent), gastric cancer in 5 (2.5 per cent), cancer of other portions of gastro-intestinal tract in 2 (1 per cent), vague gastric symptoms in 13 (6.5 per cent) we find that ulcer symptoms are 5 times as frequent in the families of ulcer cases as in those of non-ulcer patients. Especially significant is the multiple occurrence of gastric carcinoma in the families of ulcer patients. In 121 ulcer patients' families there were 18 cases of gastric cancer—that is, every 7-8th ulcer patient showed a family history of gastric carcinoma. In the families of non-ulcer patients only every 40th gave a family history of carcinoma. Spiegel, therefore, concluded that the frequency of gastric disease, especially of gastric carcinoma, in the families of ulcer patients speaks for the important role played by constitutional organ inferiority in the pathogenesis of peptic ulcer. He does not conclude that all gastric and duodenal ulcers arise on the basis of a definite constitutional type, but that a certain proportion of such ulcers are definitely associated with the asthenic and lymphatic constitution. Siemens thinks that the rôle of the idiosyncrasy in the origin of peptic ulcer is not wholly clear. On the other hand Strauss believes that one-third of his cases show a definite familial occurrence. Grote makes a still stronger statement; he found evidence of a familial incidence

of ulcer in two-thirds of his cases. Bauer and Aschner believe that the constitutional susceptibility to peptic ulcer is recessive in character. The general constitutional peculiarities of individuals with gastric ulcer have been described by numerous writers. As early as 1913, Martius attempted to explain gastric ulcer on the ground of a spasmogenous etiology, associated with a definite constitutional factor "a spasmophilic disharmony of the vegetative nervous system," Czernicki also noted the incidence of ulcer in association with an asthenic-neuropsychopathic constitution. Strauss also noted constitutional peculiarities in the families of patients with peptic ulcer, especially the occurrence of a eunchooid or adiposogenitalis type. Constitutional anomalies endocrinal in nature are apparently more frequent in families showing a hereditary "weak stomach". They may exist without other characters of an asthenic constitution in the form of gastric neuroses or a neurodysergy. Bauer notes the association with peptic ulcer of constitutional arterial disease, hyperacidity, lowered vitality of stomach wall, vasomotor excitability, motor disturbances secretory anomalies and various anomalies of the muscosa. In this country but little contribution has been made to the constitutional aspects of peptic ulcer. With all of the enormous clinical material of peptic ulcer seen by the Mayos, Smithies and others, their writings upon this subject are singularly devoid of any observations bearing upon familial occurrence or association with constitutional peculiarities. The same thing is true of

the surgical histories of ulcer cases in the average American hospital. Taken usually by internes or inexperienced young assistants who lack any broad conception of constitution or constitutional peculiarities these important facts do not appear in these histories, and they are worthless as far as throwing any light upon the hereditary peculiarities of a given patient's family. Moreover, it is a mistake to try to obtain such facts from the patient himself. The writer has had the experience of receiving the clinical histories of ulcer and cancer cases, in which it was stated that the "family history is negative"; and then on inquiry from members of the family has found that the said family presented multiple cases of ulcer or cancer. In every one of the cases of peptic ulcer with which he has come into direct contact, he has found abundant evidence of the familial occurrence of gastric or duodenal ulcer, gastric cancer, or gastric disturbances associated with other anomalies of constitution. The familial "weak stomach" belief so firmly entrenched in the layman's mind has a definite foundation of fact underlying it. In this country, the academic discussion of the etiologic relationship of peptic ulcer to gastric cancer has received undue prominence and obscured the much more important constitutional aspects of this disease.

UNITED STATES PUBLIC  
HEALTH SERVICE

*Seasonal Prevalence of Tularaemia.*

Seasonal incidence of cases of tularaemia, according to the United States Public Health Service, is due to the seasonal variation of three sources

of infection, tick bite, fly bite and the dressing of wild rabbits, but owing to the overlapping of these influences, cases have occurred in the United States in every month of the year. The great reservoir of infection and the greatest source of human infection from tularaemia is the wild rabbits, jack, cottontail and snowshoe varieties, but owing to the agencies of blood sucking insects common to rabbits and man, we find cases resulting from tick bite and fly bite.

Of the rabbits offered for sale in the Washington, D. C., market in the winters of 1923, 1924, and 1925, Dr. Edward Francis of the Public Health Service examined the livers of 1,000 and found 9, or slightly less than 1 per cent, infected with tularaemia. The liver and spleen of an infected rabbit are studded over the surface with small spots varying in size from that of a pinpoint to one-sixteenth inch in diameter. Of 22 cases of tularaemia in Washington, 17 of the patients had dressed wild rabbits bought or sold in the market, 4 had dressed rabbits shot nearby, and one had dressed a rabbit which he had killed with a club.

Four hundred and twenty cases of tularaemia have been reported, of which 17 have died. This places the mortality at about 4 per cent. These figures embrace only the cases which have been reported to the Public Health Service, but considering the newness of the disease, they probably represent only a portion of the actual number of cases and deaths.

Cases have now been reported from Japan, from the District of Columbia and from 37 States. The nine north-

eastern States being the only significant portion of the United States in which cases have not been recognized.

As a rule when the infection has come from a rabbit some injury has been inflicted on the hand while dressing the rabbit, although a manifest injury is not necessary for infection to occur. Usually an ulcer develops at the site of infection accompanied by enlargement of the lymph glands which drain the ulcer. Fever is always present and continues for two or three weeks. The site of infection from tularaemia may be located on any part of the body other than the skin of the hands, if due to tick bite or fly bite. The diagnosis of tularaemia is confirmed by a blood test. One attack confers immunity in man. Rest in bed is the most important treatment. The enlarged lymph glands should be opened only after pus has definitely formed.

The infection has never been found in nature in domesticated rabbits raised in rabbitries.

No preventive vaccine or curative serum has yet been perfected, nor has any special drug been found effective against tularaemia.

Rabbit meat thoroughly cooked is harmless for food, and it has been found that a temperature of 56° Centigrade, of 133° Fahrenheit kills the germ of tularaemia. The ordinary disinfectants are effective. Rubber gloves should be worn by those who dress wild rabbits. Immune persons should be employed to dress them where possible. Infected rabbits, kept frozen for thirty days, have been found to be free from infection. Market inspection of

rabbits is impracticable, because only about 10 per cent of the rabbits found in the market still have the liver in place.

Beware of the wild rabbit which the dog or cat has caught, or which a boy has killed with a club,—it is probably

a sick rabbit. The hunter should not shoot his rabbits at the point of his gun. Let him be a sportsman and shoot them on the run at 5 yards, say, and the chances will be lessened that the rabbits he bags will be sick with tularaemia.

## Abstracts

*Observations on the Cause of Gall-bladder Contraction and Evacuation.* By A. C. IVY and ERIC GOLDBERG (Proc. of the Soc. for Exper. Biol. and Med., January, 1928, p. 251).

In a previous communication these writers had shown that purified extracts of the duodenal and jejunal mucosa when injected intravenously cause the gall-bladder to contract and to exert pressure on its contents and at the same time excite the pancreas to secrete. Since that report Kloster, Lueth and Ivy have made preparations the use of which indicates that "secretin" does not cause the gall-bladder to contract, but that it is some substance closely associated with secretin, because it is possible to prepare a solution of secretin which is free of the gall-bladder excitant. In more than ten experiments the writers observed the gall-bladder to contract when 20 or 30 cc. of N/10 HCl were introduced into the duodenum, the cystic duct having been clamped and the gall-bladder cannulated under barbitol anesthesia. The latent period of contraction was in most cases less than 2 minutes, whereas the latent period for the pancreatic response varied from 5 to 10 minutes. Cross-circulation experiments were performed as follows: 2 compatible dogs were given barbitol and placed on the table side by side; the pancreatic duct of each animal was cannulated; the cystic duct of each was clamped and the gall-bladder cannulated and attached to a manometer and recording tambour; the most lateral carotid of each animal was prepared for a blood-pressure record, and the medial carotids were connected with cannulae for cross-circulation. In 3 out of 4 experiments the introduction of 40 cc. of N/10 HCl into the duodenum of one dog caused the gall-bladder of the second dog to contract after a period of from 8-10 minutes.

These experiments would indicate that the introduction of the acid into the duodenum of the "first" animal caused something to enter its blood, which passed via the cross-circulation to the "second" animal, causing the latter's gall-bladder to contract. The pancreas of the second dog was only slightly stimulated in one experiment. These experiments tend to show that a hormone mechanism must be considered at least as one of the mechanisms concerned in the normal contraction and evacuation of the gall-bladder. The authors propose the term "cholecystokinin" as a designation for the principle which causes the gall-bladder to contract.

*Effect of Kidney Diet on Blood Regeneration in Pernicious Anemia.* By WM. S. MCCANN (Proc. Soc. for Exper. Biol. and Med., January, 1928, p. 255).

The experiments of Whipple and Robscheit-Robbins have shown the effects of various articles of diet on the regeneration of blood in dogs rendered chronically anemic by repeated bleeding. The most important application of this fundamental work to the therapy of anemia was made by Minot and Murphy in the administration of liver in pernicious anemia, with remarkable results that have been abundantly confirmed. It is desirable to ascertain if other foods, particular kidney and apricots, which caused active regeneration in anemic dogs, have a similar therapeutic action upon man. This paper reports the results obtained by the feeding of 250 gm. of kidney daily to two cases of pernicious anemia. The diets contained no red muscle, and no other food beside kidney known to be of high value in blood regeneration, except small amounts of apricots, prunes and other fruits, given as desserts. Both patients had remissions induced by the kidney diet. The

relative values of kidney and liver feeding can, however, be determined only through the comparison of a long series of cases.

*Origin of the Blood Monocyte.* By WILLIAM BLOOM (Proc. Exper. Biol. and Med., January, 1928, p. 244).

The monocytes of the blood were studied in normal rabbits as well as those in which a monocytosis was produced by intravenous injections of india ink, lithium carmine and saccharated iron, and by infecting the rabbit with *B. monocytogenes* recently isolated by Murray, Webb and Swan. Some of the infected rabbits were also injected with lithium carmine, while others were splenectomized. Two of the latter were slowly injected with one quarter of a cc. of Higgins' india ink in a branch of the portal vein, so that the carbon would accumulate in the endothelial cells of the liver sinusoids. Great numbers of monocytes are produced in the rabbit by the methods used. These monocytes are typical of the monocyte of the rabbit as described by Simpson and Sabin, Doan and Cunningham, etc. In all of the vessels of the animal, but particularly in those of the liver and spleen, the monocytes are always accompanied by large numbers of lymphocytes and monocytoïd lymphocytes. These latter are so numerous and form such a complete series of transition forms between the lymphocytes and monocytes that the conclusion becomes unavoidable that the monocytes develop by individual transformation of the lymphocytes. The author paid particular attention to the relations of the vascular endothelium, reticulum endothelium and fibroblasts to the monocytes, and found no evidence of any of those fixed cells turning into monocytes. The development of the fixed cells into free macrophages could be followed in his sections. Although the monocytes do not contain carmin, they can develop into carmin-staining macrophages. The evidence of the author's experiments shows that the monocytes develop from lymphocytes within the blood vessels all over the body and that the sinuses of the spleen are richest in the cells showing this transformation. The numerous mitoses in the lymphocytes in the lymphoid

tissue are sufficient to account for the numbers of new cells necessary to produce the monocytosis; there is no such increase in numbers in any of the fixed cells. When the spleen is removed and india ink injected into the portal vein, the lymphocytes in the lymphnodes and bone-marrow develop neutral red rosettes and show evidences of turning into monocytes before they leave the organs in which they are produced and before leaving the blood stream.

*General Tuberculin-like Reactions in Rheumatic Fever Patients Following Intravenous Injection of Streptococcus Vaccines or Nucleoproteins.* By HOMER F. SWIFT, CHARLES H. HITCHCOCK and CLIFFORD L. DERICK (Proc. Soc. Exper. Biol. and Med. January 1928, p. 312).

Some years ago Swift suggested that rheumatic fever had many points of similarity with tuberculosis. Since then it has been shown by him and his associates that rabbits may be rendered hypersensitive to streptococci by the production of focal lesions with various types of hemolytic streptococci isolated from rheumatic fever and other diseases. As these streptococci have been shown to belong to various immunological groups the hypothesis was formulated that if they had any etiologic relationship with the disease it was because of a peculiar type of tissue activity acquired by the rheumatic patient. They have, therefore, tested the reactivity of a number of patients in the late stage of rheumatic fever to intravenous injections of streptococci or products derived from them, heat-killed suspensions, vaccines prepared from both green and hemolytic streptococci, and nucleoproteins made from hemolytic streptococci. In all instances the initial dosage was very small and subsequently increased by slow degrees in order to avoid too severe reactions. The type of febrile reaction was uniform, and consisted, as a rule, of slowly rising temperature which usually did not begin until 6-8 hours after the injections, and often did not reach its maximum until from 16-30 hours. In a few instances the fever persisted for 2-4 days, but as a rule it has disappeared by

the end of 36 hours. There was an accompanying increase in pulse rate, often headache, dizziness and general malaise. Chills and chilly sensations were rare. In some cases there was moderate reactivation of previously quiescent arthritis, and symptoms pointing to activation of cardiac foci. These reactions are strongly suggestive of the late reactions observed in tuberculous patients after injections of tuberculosis. They are distinctly different from the non-specific shock reactions observed in control cases, and that others have observed in rheumatic patients following intravenous injection of typhoid vaccine. In the latter instance the reaction is usually ushered in by a chill within 1-4 hours after the injection; this is followed within 1-3 hours by the peak of the fever, which soon subsides. The reaction following the use of typhoid vaccine was usually completed in 10 hours or less. Small also has observed similar late general reactions 24-48 hours after subcutaneous injection of rheumatic fever patients with vaccines of *Strept. cardioarthritides* described by him. At times these reactions were very severe. In their focal features they were strongly suggestive of tuberculin-like reactions. Swift and his associates feel justified in assuming that the patients showing these peculiar general and focal reactions, following injections of these streptococci and their products, have a tuberculin-like allergy (hyperergy) towards streptococci, and that probably this altered tissue reaction accounts for many of the peculiar characters of this disease.

*A Further Study of Gye's Hypothesis on the Etiology of Malignant Tumors.* By JOHN A. KOLMER and MALCOLM J. HARKINS. (The Jour. of Cancer Research, October, 1927, p. 217).

Nearly two years have elapsed since Gye made his announcement that the cause of all malignant new growths of man and the lower animals is a filterable but cultivatable ultramicroscopic microbe, which, however, is unable to produce tumors unless the re-

sistance of the host is first specifically reduced by a second cellular product or "chemical stimulant" called the "specific factor," so designated because the latter and not the microbe was held by him to determine the kind and species specificity of tumors. No confirmation of Gye's work has up to the present time been obtained by any worker; indeed all experimental work carried out on the lines indicated by his investigations have led to results negating both his technique and his conclusions. The present paper repeats Gye's work and led to the following conclusions:

1. The infectivity of the Rous fowl sarcoma is usually completely destroyed by treating sand-paper and Berkefeld filtrates of 5 per cent tumor suspension with 5 per cent chloroform or 1:5000 acriflavine for 6 hours at 30°C., likewise by heating at 55-56° for 18 minutes.

2. Inoculation of Plymouth Rock chickens with subcultures of fowl sarcoma and 5 per cent chloroform treated filtrates have produced no tumors.

3. Inoculation with subcultures and 1:5000 acriflavin treated filtrates produced no tumors.

4. Inoculation with chloroform and heat treated filtrates produced no tumors.

5. Inoculation with acriflavin and heat treated filtrates have with one exception produced no tumors.

6. Substitution experiments employing mouse sarcoma 37/S yielded negative findings.

7. The results are interpreted as failing to confirm Gye's hypothesis on the etiology of malignant new growths.

No results were obtained in this investigation that would cause these workers to change their previous conclusion that Gye's "specific factor" is in reality nothing more than a suspension of attenuated living virus which may or may not produce a tumor depending upon the fowl's susceptibility or resistance.

## Reviews

*Practical Bacteriology, Blood Work and Animal Parasitology.* Including Keys, Zoological Tables and Explanatory Clinical Notes. A Compendium for Internists. Eighth Edition, Revised and Enlarged. By E. R. SRRR, A.B., Ph.G., M.D., Sc. D., LL.D., Rear Admiral, Medical Corps, and Surgeon General, U. S. Navy; President National Board of Medical Examiners; Member Federal Board of Hospitalization; Formerly Commanding Officer and Head of Department of Tropical Medicine, U. S. Naval School; Professor of Tropical Medicine, Georgetown University; Professor Tropical Medicine, George Washington University; Lecturer in Tropical Medicine, Jefferson Medical College; Associate Professor of Medical Zoology, University of the Phillipines. 837 pages, 1 plate and 211 other illustrations containing 683 figures. P. Blakiston's Son & Co., Philadelphia, 1927. Price in cloth, \$6.00.

In the production of this new edition the author attempted to reduce its size, but because of the important additions to our knowledge along the line of clinical pathology in the last four years, it proved necessary to increase by about the same number of pages it had been planned to reduce it. This work began as a laboratory manual in clinical pathology prepared to serve as a textbook for the student officers at the Naval Medical School, and in each revision the author has been guided by his experience in teaching, and by the criticisms of students and suggestions from the instructors at the Naval Medical School. Numerous changes have been made in the material used for this new edition. Keys have been added giving the nomenclature approved by the Society of American Bacteriologists, the old names in parentheses following the new ones. In the subject

matter the new name is given following the long accepted designation. Chapters on the methods of medical and dental cooperation practiced in the Navy and Navy Schools have been incorporated. Since the Kahn test has been made standard in the Navy since December, 1925, a comprehensive description of the method and variations, prepared by Dr. Kahn, has been incorporated. Particular attention is invited to the many additions and changes under the streptococcus group—particularly those bearing on scarlet fever, measles, erysipelas and poliomyelitis. Some of the most important changes in this edition have been in Part II, Study of the Blood. The older methods of cell counting and other technical procedures have been replaced by more recent ones. The sedimentation test is extensively discussed in this chapter. In Chapter XIV a new section on the hemorrhagic diseases has been added, with new material on sickle-cell anemia and glandular fever. In Part III the changes in zoological nomenclature have been almost as great as with the bacteria. An entirely new section on liver-function tests, prepared by Lt. W. W. Hall, has been added. The section on nutrition in health and disease has been revised by Commander Phelps; while the section on disinfectants and insecticides has been brought up to date by Setterstrom. Many other changes and additions are scattered through the book. The presentation of the abundant material is necessarily much condensed, but the main facts are presented in a clear and concise form. It is a very practical manual of clinical pathology, particularly well adapted for its main purpose—its use in the Naval Medical School and in Naval laboratory work. It is well-printed, in a convenient form; its illustrations are many and adequate. It covers such a wide extent of ground that it may



be of great use to the regular medical student and internist as well.

*Recent Advances in Tropical Medicine.* By SIR LEONARD ROGERS, G.T.E., M.D., B.S. (Lond.), F.R.G.P., F.R.C.S., F.R.S., Indian Medical Service, Ret. Physician and Lecturer London School of Tropical Medicine; Lecturer on Tropical Medicine, London School of Medicine for Women; Late Professor of Pathology, Medical College, Calcutta. 398 pages, 12 illustrations, P. Blakiston's Son and Co., Philadelphia, 1928. Price in cloth, \$3.00.

Tropical Medicine is not now making the giant strides that it did twenty-five years ago, but there has been nevertheless a definite progress made in all parts of the world. The heavy task of summarizing the more important recent advances in tropical medicine have been made possible largely through the abstracts published in the *Tropical Diseases Bulletin* and in the *Medical Annual*. The author has given especial prominence in this little book to treatment and to other points of most practical importance to the isolated man in the tropics, rather than to the minute pathology and laboratory technique, which he so rarely has the facilities or the time to make use of. He hopes that this compilation may help to lighten the labors of the scattered bearers of the white man's burden throughout the Empire. The twenty-three chapters treat in order, of Kala-azar, Dermal Leishmaniasis, Malaria, Blackwater Fever, Trypanosomiasis, Relapsing Fever, Yellow Fever, Dengue and Phlebotomous Fevers and Tick Typhus, Undulant Fever, Plague, Cholera, Bacillary Dysentery, Flagellate Diarrhea, Abiasis, Amebic Hepatitis and Liver Abscess, Sprue, Ankylostomiasis or Hookworm Disease, Schistosomiasis, Filariasis, Leprosy, Yaws, Beriberi and Pellagra. The material in these chapters is recent, well condensed and concisely presented. The convenient size of the volume makes it a very handy manual on these most important of the tropical diseases, and should be of use to the general medical student in the sub-tropical and temperate zones, as well as to the student in the Naval schools and hos-

pitals. The treatment of the material is eminently practical and general aims of the author are satisfactorily accomplished.

*Recent Advances in Haematology.* By A. PINEY, M.D., Ch.B. (Birm.); M.R.C.P. (Lond.), Research Pathologist, Cancer Hospital, London; late Director of the Charing Cross Hospital Institute of Pathology, London; sometime Lecturer in Pathological Histology in the University of Birmingham. 276 pages, 4 colored plates and 18 text figures. P. Blakiston's Son and Company, Philadelphia, 1927. Price in cloth, \$3.50.

The modest preface to this little book craves the indulgence of the reader for its deficiencies, since the writer believes that the production of an adequate book dealing with the recent advances in hematology would require an almost encyclopedic knowledge of the vast literature of the subject. He has therefore attempted only to give indications of what he regards as being the present position of a number of hematological subjects, but has not tried to include every aspect of the science, nor has he been able to make reference to all the investigators who have contributed to our knowledge of the subject. There are fourteen chapters, dealing respectively with an introduction, the reticulo-endothelial system, development of blood cells, leukemia, pernicious anemia, leukemoid blood pictures, leukemoid reactions, reticulo-endotheliosis, polycythemia, hemorrhagic diatheses, symptomatic changes, Gaucher's disease, Banti's disease, acholuric jaundice and anemia pseudo-leukemica infantum. There follow then a summary, an Appendix I, dealing with hematological technique, and a second Appendix treating of textbooks and monographs on the subject, and finally the index. The book is in truth only a manual, and possesses all of the faults of incompleteness that manuals usually show. There is a great unevenness in the treatment of the various subjects; some of these, such as polycythemia, the leukemic and aleukemic lymphoblastomas, Banti's disease, etc., being very inadequately treated. The author seems to be familiar only with recent hema-

tological literature, and, therefore, many of the important facts of hematology already recorded have escaped his notice, and he introduces other ideas as if he were the original discoverer of them, although most of them have been in the literature for thirty years or more. He has shown good judgment in his support of the modern conceptions of the familial susceptibility to pernicious anemia, to the neoplastic character of the leukemic and aleukemic lymphoblastomas and myeloblastomas, and of Hodgkin's disease; but his general treatment of the subject is somewhat amateurish, and, although readable and interesting, not very helpful from any practical standpoint. The eighteen illustrations of the book are extremely poor and might better have been omitted, for any illustrative value they possess.

*Recent Advances in Medicine. Clinical Laboratory Therapeutic.* By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Assistant Physician to the Middlesex Hospital; Lecturer in Practical Medicine, Middlesex Hospital Medical School; Sometime Radcliffe Travelling Fellow, University of Oxford; and E. C. Dodds, M.D., B.S., Ph.D., B.Sc. (Lond.), Professor of Biochemistry in the University of London; Chemical Pathologist to the Middlesex Hospital, Bland-Sutton Institute of Pathology; Chemical Pathologist to the City of London Maternity Hospital; Pathologist to the Royal National Orthopedic Hospital. Third Edition. 408 pages, 46 illustrations. P. Blakiston's Son and Company, Philadelphia, 1926. Price in cloth, \$3.50.

Three editions of this work have been necessary in two years. In this, the third, alterations have been made in the arrangement of the book. An introductory chapter has been added dealing with clinical investigations, as an indication of the value of the methods subsequently described and

their practical application. The clinical portions of the book have been expanded; a section has been added on the after-care and treatment of diabetic patients, and the graduated diets have been set out in the form of the daily meals so that their practical application is facilitated. The investigation of the condition of the gall bladder by means of cholecystograms and the use of lipiodol injections in diseases of the lungs have been described. These two sections are illustrated by X-ray plates. Further alterations and additions include the recent work on the van den Bergh test, the galactose test for liver function, and an amplification of the description of the phenoltetrachlorophthalein test for liver function. The chapter on Blood Analysis is now placed at the end of the book, and in order to make this section complete the colorimetric methods of urinary analysis have been included. The special blood examinations are now described in a separate chapter, and the article on blood transfusion has been amplified to include the recent work on blood grouping. This is of importance as showing the further precautions which have been found necessary before a transfusion is carried out to avoid the risk of death from incompatibility. This book, as it now stands, is a very valuable and convenient manual of clinical laboratory procedures, both diagnostic and therapeutic. Care has been taken to give a workable description of each procedure; all techniques described have been personally performed by one or the other author, and the accounts are taken from their note-books. While sometimes differing from the original descriptions the methods described have been used by the authors as a routine for some time and have yielded them satisfactory results. They have also attempted to evaluate the results obtained by the various tests. The guiding principle has been to describe such methods of diagnosis in a general hospital and which can be justly termed "recent advances in medicine."

## College News Notes

By direction of the President, Dr. Frank Smithies, a meeting of the Board of Regents is called for Saturday, March 3, 2:00 P. M., Roosevelt Hotel, New Orleans, La.

Heretofore the meetings of the Board have been delayed until the Clinical Session had begun, with the result that elections to Fellowship were delayed and hurried, members of the Board could not attend many of the general sessions and clinics, and insufficient time was available for the discussion and determination of College problems and policies.

Members of the Committee on Credentials are asked to meet Saturday morning, March 3, 9:00 o'clock, to examine all applications for Fellowship and prepare recommendations to the Board of Regents for disposal of the same. Any members of the Committee on Credentials who reach New Orleans Friday, March 2, are asked to arrange with the Executive Secretary to start at once on the examination of these applications, in order to facilitate the completion of this important and lengthy task.

Reservations for all members of the Board of Regents have been made at the Roosevelt Hotel.

### OBITUARY

Dr. Charles Erastus Darrow (Fellow, February 23, 1920) died suddenly in Rochester, New York, on January 2, 1928, of Angina Pectoris.

Dr. Darrow was born in Rochester on December 3, 1855. He received his early and academic education at the Satterlee Private School, of Rochester and at the University of Rochester, from which he was graduated with the degree A.B., in 1877, being also elected to Phi Beta Kappa. Later he received the degree A.M. from the same university. He studied for one year

at the Jefferson Medical College, in Philadelphia, and was graduated from the College of Physicians and Surgeons, the Medical Department of Columbia University, in 1881, with the degree M.D. He began the practice of medicine in Rochester immediately after his graduation. For many years he was one of the visiting physicians to the Rochester City Hospital, later the Rochester General Hospital, and on reaching the age of 65 years, in 1920, was made one of the consulting physicians of the hospital.

Dr. Darrow was preeminently a member of the fast disappearing group of family physicians, and retained the loyal support of a large clientele until the day of his death, which occurred during the course of his regular visits to his patients. The greater part of his work belonged to the department of Internal Medicine, although in his younger days he is credited with having devised several practical surgical instruments. He was much interested in the serum treatment of tuberculosis, elaborating a method of his own which he used in his practice for several years.

A search of the literature shows that in 1866 he contributed a paper to the American Journal of Obstetrics, entitled "A Practical Self-retaining Sim's Speculum." 19:595; and to the New York State Journal of Medicine, in the October issue of 1905, a paper entitled "Bronchopneumonia."

An editorial in the Rochester Democrat and Chronicle for January 6th said: " \* \* \* There is a type of physician who sees his profession as a great opportunity for lightening the human load. Dr. Darrow was of that type. He had the sympathy, the natural love for his fellow beings, the innate kindness that added potency to the medicaments he prescribed. These qualities, linked with a skill in his profession that commended wide attention, explain the

unaffected grief with which the large circle of his friends heard of his sudden passing."

Dr. Darrow, in addition to being a Fellow of the American College of Physicians, was a Fellow of the American Medical Association; a member of the Medical Society of the State of New York, and the Medical Society of the County of Monroe, a Fellow of the Rochester Academy of Medicine, and a member of the Rochester Medical Association and the Rochester Pathological Society.

In 1909, Dr. Darrow was elected vice-president of the Medical Society of the County of Monroe, and in 1910 its president. In 1911, at the conclusion of his term as president, he was elected a censor of the Society and served in that capacity until 1914.

(Contributed by Dr. John M. Swan,  
F. A. C. P., Rochester, New York.)

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Dr. Irwin C. Sutton, Hollywood, Calif.  
(Associate, March 10, 1923).

Died January 25, 1928; aged 31, M.D.,  
College of Physicians and Surgeons, Los  
Angeles, 1919; postgraduate study, Mayo  
Clinic and Johns Hopkins Hospital.

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#### CONFERENCE ON RHEUMATIC DISEASES

A Conference on Rheumatic Diseases is to be held at Bath, England, on Thursday and Friday, May 10th and 11th, 1928. Sir George Newman, Chief Medical Officer of the British Ministry of Health, has kindly consented to act as President of the Conference. There will be three Sessions: (1) Social Aspects, presided over by Lord Dawson of Penn, Physician to H. M. King George, (2) Causation, presided over by Sir Humphry Rolleston, (Regius Professor of Physic, University of Cambridge), and (3) Treatment presided over by Sir E. Farquhar Buzzard, (Regius Professor of Medicine, University of Oxford). The local Hon. Medical Secretary is Dr. Vincent Coates, 10, Circus, Bath, England.

#### SPECIAL ANNOUNCEMENT

The 13th Annual Convention of the Catholic Hospital Association of the United States and Canada and the Second Annual Hospital Clinical Congress of North America will be held in the Cincinnati Music Hall, Cincinnati, Ohio, June 18th to 22nd, inclusive, 1928. The Fourth Annual Convention of the International Guild of Nurses will be held at the same time, in the same building, at night meetings.

This Convention and Congress will be one of the largest and most important hospital meetings of the year, and will comprise general scientific meetings, special clinics or demonstrations of hospital departments, and three hundred special commercial and educational exhibits. Outstanding authorities in medicine, surgery, pathology, nursing, dietetics and hospital administration, architecture and engineering will lecture and demonstrate in specially planned clinics representing the various departments of the modern hospital. A professional program of the highest interest and value is now being formulated, and all persons interested in medical and hospital service are cordially invited to attend. Further information may be obtained from John R. Hughes, M.D., Dean of the College of Hospital Administration, Marquette University, Milwaukee, Wisconsin, who is General Chairman of the Convention and Congress.

#### Meeting of

#### THE AMERICAN COLLEGE OF PHYSICIANS

NEW ORLEANS, MARCH 5-9, 1928

#### PROGRAM

Corrected and Brought Up to Present Date

MORNING SESSION, MONDAY, 10:00

Address of Welcome, Mayor Arthur O'Keefe.

Address of Welcome, President A. B. Dinwiddie, Tulane University.

Address of Welcome, Dr. J. Birney Guthrie, President, Orleans Parish Medical Society.

Address of Welcome, Dr. C. C. Bass, Dean, Tulane University School of Medicine.

1. Dr. Julius Bauer, Vienna, Austria, "Adaptation and Compensation as Origin of Disorders."

2. Dr. David P. Barr, "Multiple Myeloma."

3. Dr. L. G. Rowntree and Dr. George E. Brown, "Studies in Blood Volume with the Dye Method."

4. Dr. Joseph Sailer, "Cardiac Conditions Contraindicating the Use of Digitalis."

5. Dr. Frank R. Menne, "The Effect of Iodin on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

#### EVENING SESSION, MONDAY, 7:45

1. Dr. Maud Sly, "Cancer and Heredity."

2. Dr. Aristides Agramonte, Havana, "Review of Research in Yellow Fever."

#### MORNING SESSION, TUESDAY, 10:00

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."

2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."

3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."

4. Dr. C. C. Sturgis, "The Treatment of Pernicious Anemia with a Liver Fraction."

#### Symposium on Tuberculosis.

5. Dr. Charles L. Minor, "Modern Trends in the Treatment of Tuberculosis."

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

#### EVENING SESSION, TUESDAY—7:45

1. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

2. Dr. James S. McLester, "The Influence of Latent Syphilis, So-called, upon the Course of Other Diseases."

#### MORNING SESSION, WEDNESDAY—10:00

1. Dr. Walter M. Simpson, "Tularemia: A Clinical and Pathological Study of Fifteen Non-Fatal Cases and One Rapidly Fatal Case with Autopsy."

2. Dr. L. F. Bishop, "The Practice of Cardiology."

3. Dr. Morris H. Kahn, "Heart Strain and Its Consequences."

4. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

#### Symposium on Epilepsy.

5. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

6. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

7. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

#### EVENING SESSION, WEDNESDAY—7:45

#### Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."

4. Dr. J. C. Small, "Rheumatic Fever."

#### MORNING SESSION, THURSDAY—10:00

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."

2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."

3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the View Point of an Internist."

## Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."
5. Dr. Frederick M. Allen, "Present Results and Outlook of Diabetic Treatment."
6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."
7. Dr. W. H. Olmsted, "The Dietetic Management of the Diabetic in the Doctor's Office."

## MORNING SESSION, FRIDAY—10:00

1. Dr. J. L. Goforth, "Natural and Acquired Body Resistance to Neoplasia."
2. Dr. T. Z. Cason, "The Progress of Medical Research in the South."

## Symposium on Tropical Medicine.

3. Colonel Roger Brooke, "The Influence of the Tropics on Rickets."
4. Dr. Aldo Castellani, "Metadysentery, with Remarks on the Classification of Intestinal Bacteria."
5. Dr. Wm. M. James, "The Early Lesions of Intestinal Amebiasis."
6. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.
7. Dr. Aristides Agramonte, "Considerations upon the Etiologic Agent of Yellow Fever."

## EVENING SESSION, FRIDAY—7:45

1. Dr. Julius Bauer, Vienna. Convocation Address—"Multiplicity of Factors in the Etiology of Disease."

January 17, 1928.

Dr. E. R. Loveland, Executive Secretary,  
The American College of Physicians,  
Philadelphia, Pennsylvania.

Dear Dr. Loveland:

You will recall that the Governor, the Mayor-Municipality, the Medical College of Virginia and the Richmond Academy of

Medicine presented invitations to the American College of Physicians, at their meeting in Detroit, asking that the 1928 convention be held in the unique, historic city of Richmond, which is also one of the most prominent medical centers in the South.

We are still desirous of having our City and State honored with one of your meetings and want to impress this upon those having the selection of the city for the 1929 meeting.

Many of the scientific branches of medicine and surgery, with organized units, have honored Richmond and all of them have expressed themselves most generously with the cordiality, hospitality and success of the meetings.

We have a Medical College, the oldest in the South, which is preparing to enlarge extensively; many standard hospitals and a city unique with a background of history and many shrines of interest particularly to those engaged in science in the spirit of the American institutions.

Six trunk-line railways lead to Richmond and several of the national highways traverse some of the most beautiful sections of our country and in line with many other points of interest in our City and State.

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I feel sure, should Richmond be honored, that you will find every agency with open hands and hearts ready to facilitate and cooperate in any way possible to make the occasion one of unusual success.

Very truly yours,

Richmond Chamber of Commerce

W. T. Dabney, Business Manager.



# Gastro-Duodenal Hemorrhage\*

By FRANK SMITHIES, M.D., Sc.D., *Chicago, Illinois*

**B**LEEDING from the stomach may be acute and copious or chronic and of small amount. Both forms of hemorrhage may be continuous or intermittent. A combination of the grades is possible. Sudden, copious gastric hemorrhage commonly leads to blood vomiting (*hematemesis*) and to blood-stained stools (*melena*). However, even extensive gastrorrhagia may be unaccompanied by hematemesis, but may be associated with melena alone. Chronic seepage of small quantities of blood is, of itself, rarely productive of hematemesis. While this form of gastrorrhagia may give rise to obvious melena, quite commonly the presence of blood pigment in the stools can only be demonstrated by chemical, microscopic or spectroscopic tests (so-called "altered" or "occult" hemorrhage).

## *Case-Briefs Illustrating Clinical and Pathological States Associated with Gastrorrhagia.*

Case I.—A male, aged 49, had been annoyed for two years with a gradually increasing painless dysphagia. Recently, solids lay "like a lump of lead at the pit of the stomach" and fluids were swallowed and retained only by vigorous and continued gulping manoeuvres. Suddenly following the ingestion of peanuts at a ballgame, large quantities of dark red, unclotted blood were vomited; bleeding persisted,

exsanguination seemed imminent and the man was brought by police ambulance to the hospital.

Physical examination was negative apart from signs attendant upon acute hemorrhage, with the exception of a moderately large, hard, rough-surfaced liver. A working diagnosis of non-malignant obstruction at the cardia, in association with cirrhosis of the liver was made. Later, lues was proved, hepatitis established and fibrous stenosis of the lower esophagus demonstrated.

*The hemorrhage was attributed to rupture of sinus-like veins near the cardia. Specific therapy was pushed. The patient is alive and rugged after eleven and one-half years. A moderate degree of dysphagia persists.*

Case II.—A male, aged 64, who had been subjected to long duration radium treatments for suspected cancer of the prostate gland, and following which was "greatly prostrated and hospitalized for this" for sixteen weeks, on arising one morning, experienced sudden dizziness, "pounding of the heart" and, without any pain, vomited a large amount of fluid and clotted blood. Under rest and starvation bleeding ceased in three days and never recurred. A month afterwards, painless hematuria appeared and persisted for a week. The catheterized urine contained, in addition to blood cells, practically a pure culture of non-hemolytic

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streptococci in short chains. Six weeks after the hematuria the man became febrile, the attack lasting several days, he had pain in the left axillary zone and coughed up bloody mucoid material for a week.

Physically, the axillary region exhibited an irregular area of airless lung tissue, fine moist râles, but no well-defined consolidation. The bloody sputum contained non-hemolytic streptococci in clumps and short chains.

When examined by the writer a heart in early decompensation was present, the myocardial weakness being aggravated by an advanced mitral regurgitation. Blood culture made on the third day of a febrile stage of the patient's illness showed, after four days, non-hemolytic streptococci growing in short chains.

*Explanation of the gastric hemorrhage* appeared to lie in this man's being affected with a subacute bacterial endocarditis from which septic emboli were carried away in the blood stream, producing embolism successively in the gastric wall, the kidney and lung (infarction).

Case III.—A female, aged 24, was admitted during a most alarming gastric hemorrhage. She was in good flesh, very restless, apprehensive and loquacious. She was menstruating profusely at time of entry. The gastrorrhagia had appeared following severe epigastric pain.

The abdomen exhibited 4 surgical scars: two in the upper right quadrant, one in the right lower quadrant and one above the pubis. There was a history of five abdominal sections: an appendectomy, a uterine "suspension," an operation for "ovarian cysts," a plastic operation upon the pylorus for suspected peptic ulcer (no ulcer demonstrated) and within the past year, a gastroenterostomy for suspected "hidden ulcer" (none demonstrable).

The operative procedures were carried out to relieve dysmenorrhea and, during the past four years, a digestive disturbance. In association with the dyspepsia, over a period of three years, there had been nine severe gastric hemorrhages. *These hemorrhages had always occurred during or*

*before a menstrual cycle.* Peptic ulcer had been diagnosed—several Leube-Sippy treatments had been instituted with no benefit and finally surgical exploration had been performed. Careful search failed to reveal peptic ulcer, but operative procedures were performed "on suspicion." Three hemorrhages, excluding the one for which the patient came under our observation, had occurred since the pyloric plastic surgery and the gastroenterostomy.

*Explanation of the gastrorrhagia:* a "vicarious" bleeding, supplementing menstruation.

The patient was advised regarding the nature of her ailment; matrimony and child bearing were suggested. Her subsequent history was another severe hemorrhage, for which one-third of the stomach was removed "on suspicion." While convalescing from the pylorotomy, menstruation occurred, and with it, a most copious hemorrhage. The patient finally married, quickly became pregnant and since pregnancy, has experienced neither dysmenorrhea of gastrorrhagia. She has borne four children in seven years.

Case IV.—A male, aged 36, experienced vague gastric discomfort, became dizzy and vomited a large volume of fluid and clotted blood. A diagnosis of peptic ulcer was made and a Leube-Sippy regime instituted. Soon after leaving the hospital "cured," another copious hematemesis occurred and the patient came under our care.

Physically, apart from signs of severe blood loss, there were demonstrated a firm, tender spleen extending a hand's breadth below the left thoracic margin, an enlarged, smooth-surfaced liver, palpable for three fingers-breadth below the ribs and a tender area over the anatomic region of the gall-bladder. The stool contained entameba histolytica. The anemia was of "secondary" type; there was blood-derived pigment in the urine. By x-ray and otherwise, the alimentary tract was entirely negative.

The patient gave history of serving as a soldier in the Spanish-American War. In Cuba he experienced malaria and "dysen-

tery." He had been anemic since these affections.

*Explanation of Gastrorrhagia:* Splenic anemia and Banti's syndrome (chronic malaria? systemic amebiasis?).

The subsequent history included splenectomy following an exsanguinating hemorrhage; blood transfusions; cholecystectomy and later operation for common duct stones; treatment of intestinal amebiasis. The patient lived and was active as a physician for more than twenty years, but recently died from uncontrollable gastric hemorrhage.

Case V.—A female, aged 23, appeared for the relief of several attacks of vomiting of material which "looked like red ink." The emesis was painless but was preceded by nausea, full feeling in head and dizziness. The patient is a chemist and for several months has been conducting research upon very volatile oil distillates. She had no vomiting or other digestive disturbance prior to engaging in her present research.

Physically, the girl appeared pale, rather bluish and without energy. On exertion there were breathlessness and cardiac palpitation. She was in good flesh and objectively there were no evidences of any ailment of the alimentary tract. The hemoglobin was 45%, r.b.c. 3,600,000, leucocytes 11,800. Blood films exhibited no atypic red cells, but there were many fragmented corpuscles. The fragility test revealed a ratio nearly double the normal. The urine was pinkish red, gave test for blood pigment but contained few red blood cells. A tube passed into the stomach secured more than 500 c.c. of almost carmine colored water fluid and a small quantity of food. This material gave positive blood pigment tests. All other clinical and laboratory tests were negative. The blood serum appeared pinkish. No spectroscopic observations were possible.

*Explanation of "gastrorrhagia"*—Chronic poisoning by volatile hydrocarbons (naphtha, benzene, xylol, etc.)—accompanied by intermittent blood lysis intravascularly—capillary dilatation and the appearance of

laked blood in gastric contents and urine—toxic gastrorrhagia.

Change of occupation, blood transfusion and the feeding of high vitamin diet and cod liver oil restored the patient to health.

Case VI.—Male, aged 27, brought to the hospital in collapse. The evening previous to entrance, while the patient was reaching for the reins over the dashboard of a buggy, the horse became alarmed and kicked violently. The dash-board was smashed and the patient was struck in the epigastrium and knocked from the carriage unconscious. When he gained consciousness, he experienced excruciating epigastric pain and vomited large quantities of red blood. Under morphia, vomiting ceased and the patient became comfortable. However, frequently thready pulse, pallor, sighing respirations, with later shock, progressed rapidly.

The patient was comatose at examination, pale, cold and sweaty. There was a swelling in the epigastrium, and the upper abdomen exhibited board-like rigidity. While arrangements were being made to transfuse the patient preparatory to exploratory laparotomy, he expired.

Autopsy revealed a ragged tear in the anterior wall of the stomach, freely bleeding vessels and the peritoneal cavity partly filled with blood serum and clotted blood. Traumatic gastrorrhagia.

Case VII.—Male, aged 54 and weighing more than 250 pounds, had attended a Christmas Eve dinner at which he had not eaten very generously, but had partaken freely of alcoholics. Two hours after dinner he experienced acute knife-like agonizing mid-epigastric pain, and began to vomit, first food admixtures, and later great quantities of fluid and clotted blood. A diagnosis of "acute indigestion" was made, but the patient, even after vomiting was controlled, sank into shock rapidly and was brought to the hospital.

Examination revealed a heavy florid type individual, with shallow, stertorous respiration, cyanosis and cold, clammy extremities. The epigastrium was distended, and there was an indefinite mass palpable directly above the navel. There was begin-

ning rigidity of the abdominal wall. Gastric lavage returned large, liver-like clots. The heart tones were feeble, the rate frequent, the pulse thready, and systolic blood pressure, in spite of general sclerosis, barely 100.

A diagnosis of acute perforation of peptic ulcer, with involvement of the pancreas, was made. The patient died before midnight.

Autopsy disclosed gall-stones and acute hemorrhagic pancreatitis, the entire pancreas exhibiting apoplexy-like hemorrhages. Fat necrosis was extensive.

Case VIII.—A man aged 56 telephoned from an hotel, requesting a prescription to relieve his dyspepsia. He was informed that no treatment could be given unless he were examined. He refused examination, but later in the day again telephoned and requested to be given medicine to relieve what he called "sour stomach." He was refused, and told to present himself for examination. He finally did so, and when he appeared, seemed in pretty fair general shape except that he seemed somewhat pale and tired. He had had no pain, but on account of "sour stomach" had broken the journey on the way from Grand Rapids to his winter home in the south, believing that a short rest would prove beneficial.

Physical examination disclosed practically nothing except a rather noticeable fullness in the region of the stomach and a moderate pallor of the skin and mucous membrane. A stomach tube was passed with the idea of therapeutic gastric lavage. About three quarts of fresh blood, with moderate sized clots, were recovered. After the gastric lavage, local protective tenderness was elicited in the region of the duodenum. The patient gave a history of duodenal ulcer, and had recently been "cured" by the Leube-Sippy regimen in a hospital. (Later roentgenologic examination confirmed the diagnosis of duodenal ulcer).

Explanation of hemorrhage can be found in an acute recrudescence of a quiescent ulcer, with involvement of a fairly large artery in the base of, or adjacent to, the ulcer. The rapid filling of the stomach

with blood may have been a means, mechanically, to control hemorrhage by pressure, particularly since this patient did not vomit.

Case IX.—A male, aged 44, who had been on "gastric ulcer treatment" for two years, suddenly experienced acute pain below the right rib edge, the pain radiating to the spine in the upper lumbar region. Associated with this pain was produced emesis of blood-stained food admixtures, and later bright red blood. There were no attendant shock and pain following the vomiting, but the patient's feeble pulse and dizziness resulted in his being brought to the hospital.

Physical examination disclosed an aortitis, an early cardiac dilatation, a palpable liver, and local tenderness in the right upper abdominal quadrant. After entering the hospital, the patient again vomited and the vomitus was made up wholly of fluid red blood.

A tentative diagnosis of non-obstructing duodenal ulcer was made, and the patient treated accordingly by rest, starvation and blood transfusions. He made an uneventful recovery. The Wasserman test later was shown to be positive. Roentgen examination indicated a thick-walled stomach (cirrhosis?) and a duodenal deformity, evidently an ulcer.

Explanation of hemorrhage appears to lie in acute rupture of a sclerotic arteriole in the base of an ulcer, whose mucosal surface previously had been protected by scar.

Case X.—A full-blooded male, aged 25, who had taken several "cures" for "gastric ulcer" and who apparently was in excellent health, strength and comfort, late at night, suddenly experienced acute right upper quadrant pain and rapidly sank into a semi-comatose state.

When seen he was in shock and there were evidences of an effusion into the upper part of the greater peritoneal sac. Exploratory laparotomy disclosed a stomach full of clotted blood (there had been no vomiting) and a duodenal ulcer which had perforated into the peritoneal cavity; a small spurting arteriole was present toward

the old ulcer base. Dr. Ralph Kordenat treated the perforated ulcer by suturing and enfolding and performed gastroenterostomy. The patient made an uneventful recovery.

Case XI.—A man, aged 72, came from Montana to Chicago to attend the stock show. Shortly after his arrival, without warning and without pain, he began to vomit large quantities of red blood, and was hurried to a hospital. He gave a history of having been treated for "gastric ulcer" forty-two years previously, and since that time, had been in excellent health.

Abdominal examination revealed nothing abnormal. The patient was in fair flesh, but rather pale, and was a marked arteriosclerotic. Blood pressure (even after much bleeding) was systolic 182, diastolic 110.

Bleeding could not be controlled by ordinary means, so the patient was explored. A thick callous plaque-like ulcer occupied the posterior wall of the duodenum, about two inches distal to the pylorus, in which space there was found a bleeding artery. A modified Heineke-Mikulicz, with gastroenterostomy, was performed. The patient made an uneventful recovery.

The interesting features of this case were the long period of quiescence of an old ulcer, the general arteriosclerosis and the re-appearance of almost fatal bleeding in an ulcer so many years after ulcer dyspepsia in early life.

Case XII.—A male, aged 58, came from the Michigan Peninsula on account of dyspepsia of ulcer-like type. Three years previously, he had had a gastroenterostomy performed at a large clinic for duodenal ulcer. Following the gastroenterostomy, during the succeeding two and one-half years he had experienced three very severe hemorrhages, with bloody emesis and pronounced melena. During the past month a dyspepsia of mild retention type had been present, and the patient has felt unaccountably weak and restless.

At examination of the abdomen, there was a finger-like ridge palpable above and to the right of the navel. It was slightly tender to pressure. The stomach seemed somewhat dilated. The stool contained four

plus blood by the benzidin test. Within a few hours after the patient was first seen, he had severe right upper quadrant pain and vomited much blood. Exploratory laparotomy, under local anaesthesia, was performed, and a mass as large as a lemon occupying the first portion of the duodenum was revealed. The stomach and jejunum were filled with clotted blood. The gastroenterostomy stoma was wide open. The pancreas was firm, and there were enlarged lymphnodes above the pylorus. Involvement of the pancreas prevented surgical removal of the pyloric tumor. For three weeks, the patient bled almost constantly: hemorrhages could not be controlled by transfusion, starvation, rest or other agents. Symptoms of colon obstruction appeared, and a second abdominal exploration was made with the object of performing colostomy. The pyloric tumor which previously had been as large as a lemon had grown rapidly, involving not only the pancreas, but the liver and the transverse colon near the hepatic flexure. The mass had perforated into the colon. The patient died thirty-six hours following the second operation.

The interesting features of this case are a duodenal ulcer, whose progression apparently was not halted by gastroenterostomy; the extension of the duodenal ulcer to the pylorus, with later malignant transformation at the gastric edge of the ulcer; the frequent hemorrhages (after gastroenterostomy); the rapid extension of the tumor mass with early involvement of adjacent viscera.

*Etiology*—From the above case briefs, it will be recognized that since the pathology and functional disturbances concomitant with the appearance of blood in the vomitus or the stools are of various nature, an adequate conception of matters is essential before management is considered. Suddenly, copious bleeding from the stomach is commonly the result of accident or is a complication of a previous lo-

cal, general or constitutional ailment. It may be so acute and extensive as to prove rapidly fatal (about 2% in primary gastric bleeding). Moderate or abundant hemorrhages may occur at frequent or infrequent intervals. There is often a peculiar tendency to recurrence. The quantity of blood lost at each occasion may vary greatly in a given case.

Seepage or "occult" bleeding from the stomach is generally associated with primary progressive pathologic changes in the gastric mucosa, or is a secondary local manifestation of a systemic or constitutional fault.

In the different types of gastrorrhagia, the histo-pathologic condition of the stomach mucosa varies from simple, capillary congestion associated with local or general rupture (or diapedesis?) of minute capillary net works, to extensive loss of surface epithelium with destruction of the layers of the stomach wall and the erosion of large blood-vessels. Either process may begin intramurally, in which event the mucosa first suffers, or extramurally, when the blood vessels primarily are attacked. There is a type of gastrorrhagia which periodically occurs in females, in definite relationship to the menstrual cycle, where copious hematemesis is associated with no demonstrable gastric pathology. In the hematemesis accompanying certain anemias, infectious ailments, acute and chronic systemic toxic states or following operations upon intra-abdominal viscera other than the stomach or duodenum, there may likewise be no grossly apparent injury to the stomach mucosa.

Gastrorrhagia is associated with hematemesis or melena, or both, as follows:—

(a) In primary gastric disease, acute or chronic gastritis, simple or phlegmonous, acute gastric erosion, acute or chronic benign ulcer, *ulcus carcinomatosum*, carcinoma, sarcoma, syphiloma, tuberculoma, polyposis, ulcerated gastric cirrhosis, varicosities or aneurysm of intrinsic gastric arteries or intramural parasite (*echinococcus*, nematodes).

(b) In conjunction with chronic disease of the heart or blood vessels.

(c) Complicating chronic disease of the liver or gall-bladder or ducts (cirrhosis, neoplasm, portal thrombosis, Banti's disease, cholelithiasis, cholecystitis).

(d) Disease of the spleen (chronic splenitis, leukemia, Gaucher's spleen).

(e) Malfunction of the pancreas (acute and chronic pancreatitis).

(f) Toxemias associated with ailments of the kidney, central nervous system, thyroid gland, adrenal, hemolymph nodes.

(g) Bacteriemias or protozoemias (typhoid fever, smallpox, measles, malaria, yellow fever, cholera).

(h) Chemical poisons (phosphorus, hydrocyanic acid, volatile hydrocarbons, split-proteins and their products), and probably following burns upon the body surface.

(i) Local injury: (1) Trauma from falls, foreign bodies, blows, crushing injuries or stab wounds; (2) poisons introduced by mouth.

(j) Disordered blood states: Hemophilia, purpura, chronic anemia ("sec-

ondary" or "pernicious"), acute or chronic cholemia.

(k) In connection with certain neuropathic states, as hysteria, angioneurotic edema, tabetic crises, epilepsy, progressive paralysis.

(l) In association with physiologic cycles of females, as the catamenia and climacteric.

(m) Following operations upon organs other than the stomach, particularly when such operations are intraperitoneal.

(n) Blood may enter the stomach from a diseased lung, esophagus, adjacent viscus (duodenum, jejunum or colon by fistula) or great vessel.

#### *Morbid Anatomy in Gastrorrhagia—*

Gross or microscopic alterations in the stomach wall bear out an irregular relation to the quantity of blood present in the viscus, vomited or passed by the bowel. Abundant, even fatal hemorrhage may occur and yet no visible cause of such can be demonstrated in the mucosa. This phenomenon may exist where profuse bleeding is associated with infectious disease, cirrhosis of the liver, surgical operations not on the stomach, hysteria, burns on the surface of the body, blood dyscrasias or traumata to the abdominal wall. Commonly, however, gastrorrhagia occurs in connection with some type of peptic ulcer, or carcinoma, and in such ailments fissures, granulating ulcer edges or necrotic tumor areas can be noted in more or less definite relationship to blood-vessels.

After severe hemorrhage the stomach mucosa appears pale, yellowish-pink, often with scattered areas of

reddish-brown mottling in the mucosa and submucosa. Some grade of general edema is present. The mucosa dries rapidly when exposed to the air and then has a smooth, shiny appearance. The rugae are indefinite and the gastric wall is flabby and inelastic. When peptic ulcers bleed profusely or intermittently, local destruction of the stomach wall with perforation, protected or not protected by peritoneal adhesions, is not an uncommon occurrence. Of ulcers bleeding copiously in a series of 185, at operation or autopsy, 42% revealed perforation, actual or protected. In acute, profusely bleeding ulcers, tissue necrosis may take place rapidly, peritoneal protection is impossible and perforation may occur even before hematemesis or melena occurs. The symptoms and signs of the perforation may mask those of severe hemorrhage. At laparotomy, the stomach may be seen to be filled with clotted blood and food, while between the coils of the intestines, or in the peritoneal sacs may be found blood clots, serous fluid or pus.

Seepage of blood into the stomach is most frequently noted in connection with granulating ulcer edges, ulcerating, necrosing cancer, in achylia, primary as result of chronic atrophy of gastric mucosa, or secondary to idiopathic anemias, blood disorders or extra-gastric malignancy. With exception of the achylia, the mucosa is generally edematous, congested and bleeds readily on handling. In the achylia, the mucosa is often thin, pale and smooth. If it is scraped with a knife a pale, reddish-brown fluid can be collected, which chemically or phys-

ically can be proved to contain blood pigment.

*Signs and Symptoms of Gastrorrhagia* — (a) — *Hematemesis* — Sudden vomiting of large quantities of blood may occur without noticeable premonitory symptoms or previous evidences of disease. The vomited blood may be bright red and fluid. It is commonly mixed with undigested food and mucus. Clots may be present. They usually occur toward the end of emesis or when the blood has lain in the stomach for a time before being vomited. In general, the higher the gastric acidity the larger the clots. When the acidity has previously been low or where hemorrhage has neutralized free hydrochloric acid, coagula form relatively slowly. The quantity of blood vomited varies greatly in different patients or in the same individual at different times. The hematemesis may not represent the extent of the gastric hemorrhage. A cupful may be vomited and yet the stomach remain filled with free or partly clotted blood, which is later passed by the bowel or washed from the stomach. Such condition often leads to a sense of false security. Clots in the gastric lumen may temporarily stop hemorrhage or may mask a gradual but persistent bleeding, which, subsequently, as a result of error in diagnosis or treatment, may prove fatal. Enormous hematemesis sometimes occurs. One of our patients vomited nearly eight quarts of free and clotted blood.

Slow seepage of blood rarely precipitates hematemesis. In such instances vomiting may result from other causes. When this happens the

vomit may be colored reddish-tan, brown or even black. In advanced gastric carcinoma or in pyloric obstruction caused by an eroded ulcer, such vomitus is not uncommon.

(b) *Melena*—Practically in all instances seepage of blood from the stomach and nearly all cases of profuse gastrorrhagia are accompanied by stools more or less colored with blood or blood pigment. Where rapid loss of blood occurs, the stools may be bright red and mixed with clots. Commonly, however, the stools are dark brown or slate black. Not infrequently, abundant hemorrhage from the stomach may be unaccompanied by hematemesis, but melena may be observed either within a few hours of other clinical evidences of internal bleeding or after an interval of a day or more. Unless stools are carefully scrutinized, such hemorrhage may be overlooked, with the possibility of serious consequences.

Where seepage of blood occurs the stools may be but slightly altered in gross appearance, and unless search for blood pigment be made in the laboratory, the existence of an "occult" gastrorrhagia may remain unsuspected.

*Tests for "Occult" Hemorrhage*—In retention of stomach contents, positive "occult" blood tests are not rarely returned from the food contained therein. In such an instance, it can be seen readily that the test has no clinical value—namely, the positive tests may be due entirely to retained food in the absence of a gastric lesion, or it may be due both to a bleeding gastric lesion and to the food admixture. Similar observations apply to the making of "occult" blood tests upon stools. It is

quite necessary when making chemical tests for blood pigment in feces, to be sure that positives are not due to food stuffs or medicines (iron compounds).

Stools passed during the menstrual period are not infrequently mixed with blood. This should be appreciated particularly in the examination of stools from females.

*Examination of Feces*—For blood or blood derivatives, an analysis of stools is of considerable value to both internist and surgeon. If the analyses are not intelligently made, then the facts returned are clinically of little worth. In surgical disease of the stomach and duodenum the significance of certain special tests should be emphasized. It is not always absolutely necessary to perform some of these tests in order to arrive at a diagnosis of the ailment under investigation, but it cannot be denied that the routine performance of these analyses not only at times gives information impossible to obtain in any other way, but conveys a clearer conception of alterations taking place at the site of the disease.

*Methods of Examination*—Excepting in special instances (after severe acute hemorrhage or other emergencies) proper preparation of the patient should precede stool examination. As routine, all forms of medication should be interdicted during the time that specimens of stool are collected. Unless this caution is remembered the stool examination may be useless. Harmful deductions may be derived from the result of laboratory tests.

*Demonstration of Altered or "Occult" Blood in the Stools*.—The pa-

tient's intestinal canal should be first completely emptied by stoppage of food ingestion and where safe, by the administration of 2 ounces of *oleum ricini*. Any diet given should be free from meat products or an excess of green vegetables for two days. On the third day nothing but milk or cereal gruel should be given. On the morning of the fourth day, a saline cathartic should be administered, and the second stool passed, collected and sent to the laboratory in a covered vessel for analysis.

*Tests for "Occult" Blood*.—Numerous tests are in vogue. If the stool has been properly collected and the tests carefully performed, they are practically all of equal worth clinically. On account of abortive reactions, not infrequently given by the use of poor preparations of aloin, guaiac or phenolphthalein, routinely it has seemed to me that benzidin solutions have returned the most reliable information. The pinkish-gray powder should be used, and this should be kept in a brown bottle, carefully stoppered.

*Interpretation of Positive "Occult" Blood Tests*.—A positive response to chemical test for blood in the stool signifies only that there is a bleeding point somewhere between the lips and the external anal ring. It is thus evident that tests should be rigidly controlled and interpreted strictly in relation to the clinical history of the case. Positive tests are commonly *constant* in malignancy. They are *intermittently* present in the stools from chronic recurring peptic ulcers.

The *negative test* for "occult" blood in feces is of aid in excluding malignancy.



nancy, particularly in instances where, with a dubious clinical history, an atypic, abdominal tumor can be demonstrated.

We have not found the so-called string test, suggested by Einhorn, of reliable or of any practical value. It was positive in less than 10% of 230 proved peptic ulcers. Such clinical toys are a waste of time and effort.

*Systemic Evidences of Bleeding.*—If the hemorrhage has been of small quantity, there may be but slight physical evidences of such. Where a large amount of blood has been lost in a short time, pallor, cold clammy skin, sighing respiration, with or without rapid pulse and dilated heart, are usually evident. Frequently fainting occurs. In some instances there is delirium. The temperature is usually subnormal at first, but in fatal cases there may be an abruptly developing hyperpyrexia before death. Gastric hemorrhage is not infrequently accompanied by severe abdominal pain. Unless the hemorrhage has been sudden and severe, the discomfort produced by the pain may mask the clinical evidences of threatened shock and collapse. Patients not uncommonly suffer extensive hemorrhage without hematemesis. The blood may pass into the bowel and remain unrecognized. In these patients, shock, collapse and death may occur without the underlying causes being discovered until laparotomy or autopsy be performed. All too often, one reads newspaper accounts of death from "acute indigestion" in this class of case. In a chronic dyspeptic or in the course of an acute attack of abdominal

distress, the appearance of anemia and shock should always indicate hemorrhage until the signs and symptoms are proved to be due to other causes.

Where hemorrhage complicates the actual perforation of such gastric lesion as ulcer or cancer, the development of perigastric abscess, a general peritonitis or fistula may cloud the diagnosis.

*Prognosis*—About two per cent of instances of gastrorrhagia are acutely fatal. Oft-repeated hemorrhages occurring with a brief interval raise the total mortality to about five per cent. Sometimes the hemorrhage itself is not fatal, but death is caused as a consequence of the lighting up of infection, by a perforation with peritonitis or by heart or kidney failure.

*Management of Gastric Hemorrhage*—The clinical cases cited in this report make it evident that management of gastric hemorrhage, in order to be successful, depends upon an accurate appraisal of the condition responsible for the initiation and maintenance of the hemorrhage. Particularly does this apply with respect to operative procedures contemplated toward the abdominal viscera.

*First*, a brief history of the patient's past and present constitutional and digestive difficulties should be obtained—preferably not from the patient (except in emergencies) but from attendants or relatives. Commonly this can be done while the patient is being placed in bed or taken to a hospital. Without loss of time, especially when lesions of the abdominal viscera are known to exist or are suspected, a

hypodermatic injection of one-fourth to one-half grain of morphine sulphate with or without atropin should be made. Where hemorrhage is copious and there are marked retching and vomiting or when a patient is restless and noisy, there is no drug so valuable as morphine in physiologic doses in the emergency treatment of hemorrhage—it lowers blood pressure, slows the heart, relaxes muscles systemically and locally, quiets restless or hysterical patients and assures complete bodily rest. Much larger doses than are commonly given should be employed—even up to a half to a grain every two or three hours for several doses. The main contraindication to the exhibition of large or frequent doses of morphine is slowing of the respiration to 10 or less per minute. When morphia is given frequently, atropia should be used cautiously or omitted. The too frequent exhibition of atropia results in diminished urine output or even anuria and the attendant dryness of mucous surfaces and skin are distressing to the patient.

It is not necessary to emphasize that the patient should be put to bed, and kept there, external heat being supplied liberally and the central nervous system stimulated by the head and shoulders being low. This can be accomplished by elevating the foot of the bed on ten-inch blocks. This position not only favors normal cerebral circulation but permits vomiting without effort and prevents regurgitation of vomited material into the bronchi. Particularly is regurgitation avoided if patient is inclined on to the left side

and the head placed low and turned to the left.

After this initial treatment has been instituted, with the patient stripped, there should be carried out, in every instance, a rapid physical examination, no part of the body from the head to the toes being neglected. Such examination commonly gives indication as to the source of bleeding: whether hemorrhage has resulted from venous stasis, concomitant with heart malfunction, from liver cirrhosis, pulmonary lesions, anomalies of the spleen, biliary tract and pancreas, abdominal trauma or intragastric or intra-intestinal lesions. In all instances, whether or no an abdominal focus of disease is located or suspected, the patient or his relative should be questioned with regard to the hemophilic taint.

The blood pressure always should be taken, not only to secure a relative appraisal of deficiencies of heart strength and blood volume, but in order to establish a point from which subsequent blood pressure readings may be contrasted in patients who go into shock or continue to bleed.

Should the patient be in a hospital, complete blood counts should be made immediately and the blood clotting time estimated by such reliable procedure as that of Thomas Boggs.

If vomiting is copious, and particularly if it is accompanied by much retching and the appearance of large blood clots, then by means of a large bulb-free stomach tube, thorough lavage should be performed with normal salt solution at a temperature of 110° Fahrenheit, as suggested by the late Dr. Rodman. This procedure is remarkably efficacious in stopping hemor-

rhage and putting the stomach at rest. So long as large clots are in the stomach, peristaltic activity will continue in an effort to get rid of or digest them. Such mechanical activity on the part of the stomach interferes with protective clot formation at the site of intragastric bleeding. The heat of the lavage solution acts as an admirable hemostatic agent. In cases of actual or potential perforation, the emptying of the stomach lessens the danger of peritoneal contamination by free food residues and blood. Where frank perforation has existed, free lavage after Rodman's method, with the patient in a partial Trendelenberg position, rapidly empties the stomach and renders subsequent operative procedures less hazardous. Our experience with lavage by heated solutions in patients exhibiting gastric hemorrhage is extensive: we have never observed any harmful effects. In many instances, it has seemed that lavage after this fashion served as a life saving measure.

*Topical applications to the abdomen.* Many years ago, I abandoned the routine application of ice-bags and ice water-coils to the abdomen in patients where hemorrhage was suspected of coming from gastric or duodenal lesions. In our opinion and from our clinical experience, the local application of ice is detrimental: it chills an already shocked patient, systemically as well as locally; it lowers body temperature and interferes with adequate central nervous system function; it has relatively little, if any, effect toward "constricting" blood vessels or capillaries and thus lessening bleeding—in fact, quite likely continued cold

applications paralyze the vascular neuromuscular mechanism and by preventing normal constrictor action, prolong a hemorrhage which otherwise might cease spontaneously. One has but to scratch his hand and place over the bleeding scratch a piece of ice in order to prove how long bleeding continues following cold applications. Only in instances where physical examination indicates that perforation actually is taking place or has occurred and the peritoneum has been subjected to mechanical or infectious traumata, do we employ cold abdominal applications. In such circumstances they are used in an attempt to immobilize a part and to lessen peritoneal engorgement. Frequently such measures permit limitation of an inflammatory process to such extent that later, at an opportune time, abdominal exploration may be performed safely.

For years, I have favored extremely hot moist applications over a suspected bleeding focus. Usually these applications were employed as hot compresses rather tightly bound upon the abdomen and frequently renewed. The tight fixation of the compresses limits the motion of the abdominal wall and lessens visceral peristaltic activity. The heat prevents shock; possibly it has a derivative action upon the capillary bed and if the compresses are sufficiently hot and moist, stimulates blood coagulation. The advantage of heat over cold as an agent toward improving the patient's feeling of well being, is self-evident.

*Food.*—Mouth feeding in all its aspects should be strictly interdicted. So long as the patient is ingesting mate-

rial into his stomach, gastric peristalsis is stimulated, and with this stimulation of peristalsis, permanent clot formation is attained with difficulty. The sucking of ice, the drinking of ice water, the administration of such hemostatic agents as adrenalin solutions (liquid, gelatine or otherwise) or the effort to improve nourishment by exhibiting gruels, soups or so-called "ulcer diets" can be productive only of harmful effects. An empty stomach rapidly becomes peristalsis and secretion free, and if the viscus remains empty for longer than twelve hours, muscular contraction of the wall mechanically compresses bleeding capillaries or arterioles and lessens or completely stops hemorrhage. All too often, attempts at feeding or to administer medicinal and dietetic ulcer regimes initiate or prolong emesis and aggravate the local pathologic condition responsible for hemorrhage. If bleeding is due to such local pathology as peptic ulcer, and if hemorrhage has been repeated or is continuous, one must recall that perforation is a strong possibility; hence attempts to administer food or medicine by mouth are a potent influence toward precipitating perforation. This observation can be substantiated readily by a short residence at any busy gastroenterological or surgical clinic. There is no doubt that many patients who succumb suddenly to "acute indigestion" are instances where the cause of death is acute perforation of an ulcer or cancer; and this most serious accident would have been avoided had "routine" ulcer treatment orders, so common to many hospitals, *not* been carried out. It is our practice not only

*not* to administer water, food or therapeutic agents by mouth during the progress of gastric hemorrhage, but to interdict anything but small sips of very hot water for at least four days after definite proof is available that hemorrhage has ceased and that the local abdominal examination indicates that peritoneal involvement is not present.

*Nourishment* for the first few days of gastrorrhagia, unless the patient is in extremely low general physical condition, is not especially needed, provided measures are directed to maintaining body fluids. McVicar and others have shown how essential it is that body fluids which are lost by hemorrhage or by persistent vomiting be replaced, if one is to avoid toxic crises. We have never hesitated early to increase the fluid content of the body by all known available routes; intravenously, subcutaneously or per rectum. Commonly, sufficient fluid can be given per rectum by the Murphy drip to replace fluid lost by bleeding, to prevent renal stagnation, to keep moist the mucous surfaces, particularly of the mouth and to counteract shock. For more than ten years, we have employed as a nutrient enema the following: 8 ounces of normal salt solution; 50 c.c. of glucose syrup and 30 cc. of 50% alcohol. This is administered, at body temperature, and by the Murphy drip. The whole quantity generally is given four times within twenty-four hours. Medicinally, agents such as atropine, bromide, morphine, digitalis or even calcium may be added to these *enemata* with beneficial results. Where the blood

coagulation time is delayed, and bleeding, particularly profuse seepage of blood, occurs, we do not hesitate to give intravenously several times during twenty-four hours, 500 c.c. of one per cent solution of sodium bicarbonate and 20 c.c. of five per cent calcium chloride. Where the patient seems to be in poor flesh, in addition to being dehydrated, the sodium bicarbonate solution is supplemented by glucose in the proportion of approximately two per cent. In instances where rectal feeding is poorly borne and where it is difficult to administer fluid intravenously, normal salt solution can be administered at convenient places, subcutaneously, in large quantities, provided local tissue pressure from administered fluids is avoided.

*Mouth-feeding should only be begun* when there is conclusive evidence that hemorrhage has stopped and has not recurred. An increasing blood pressure, a faulty pulse rate whose quality is improved, a stationary or increasing red blood count and hemoglobin estimation are sufficient clinical evidence that hemorrhage no longer continues. These, especially, if the patient exhibits physical well being, is free from pain or nausea and has a flat, soft epigastrium. "Occult blood tests" may be positive in the stools for many days after hemorrhage has stopped on account of retention, and if mouth feeding is interdicted until occult blood tests are negative, then the patient is quite likely to have his resistance greatly reduced by lack of food, but, what is more important, to have his body fluids diminished below the safety point.

It is well not to feed by mouth until two days following cessation of hemorrhage. When mouth feeding is begun, then a few simple but fundamental principles should be followed: Food should be administered in small quantity frequently and, to avoid gastric spasms, should be given warm; foods which do not stimulate acid secretions should be chosen, namely, carbohydrate mixtures in preference to mixtures of protein (milk, eggs, etc.); all foods should be selected with the idea of their leaving the stomach almost immediately, in order not to excite peristalsis or locally to traumatize an injured area. One should be sure that the vitamin content of the food administered is adequate. This has been emphasized frequently by Seale Harris.

It is our policy to give milk in no form except where it is citrated or parboiled: Raw milk results in tough casein clots, and these clots excite the stomach to effort, both secretory and muscular, just as strenuously as if the patient were given meat to eat. If milk be used at all, it should be parboiled or mixed with an equal quantity of barley water, in order that small flocculent casein clots result, or to each ounce of milk one gram of sodium citrate should be added. Personally, I prefer to use very little milk or milk mixtures. Generally, our feeding routine is two ounces of water gruel (made from barley, farina, cream of wheat, oat meal, etc.), every hour, and at alternate hours an ounce of sweet fruit juice. After the first twenty-four hours, to the water gruels may be added thin custard or strained

soups, made particularly from fresh vegetables. This feeding supplies adequate vitamin demands, is readily borne, does not excite peristalsis or stimulate secretion, and its caloric value can be so computed that the patient can be built up rapidly from 400 calories to 1200 calories daily. This quantity is quite sufficient for the average individual in bed at rest. When the feeding demands are increased, then thin cereals, purees from potato, peas, beans, carrots and other vegetables and small quantities of chopped meat, particularly liver, kidneys, sweetbreads and calves' brains may be exhibited. For at least two weeks following a hemorrhage, one should be sure that the calories are kept below 3000, and that at least six feedings daily are given. Charts of pulse, temperature and blood pressure should be kept, in order that one is reassured that bleeding has not recurred. If the patient is in a hospital, certainly the hemoglobin and the blood count should be estimated every other day.

Even after the patient has gained strength and energy and is up and about, for months he should be cautioned against an excess of protein or fat (the fat slowing the emptying rate of the stomach) and should avoid "roughage feeding" in every form. After the first or second hemorrhage, patients frequently gain weight very rapidly. This should not be allowed, inasmuch as should an acute emergency arise from another hemorrhage, with or without perforation, the operative risk upon an obese individual is very grave.

Particularly to individuals who have

had hemorrhage from a bleeding gastric or duodenal ulcer, definite information regarding the nature of the ailment and its possible consequences should be given. It should be emphasized that a patient who has had one severe hemorrhage is likely to have another, and that each succeeding hemorrhage is likely to be more severe. Furthermore, the anatomic consequences of hemorrhage should be mentioned—namely, that with each succeeding hemorrhage there is a greater destruction of the gastric or duodenal wall and that it is not possible to tell when this destruction will advance to the stage where the wall of the viscus is completely destroyed and perforation result. It has always been my custom to tell a patient who has had one severe hemorrhage that he is potentially a subject for surgery. No physician is able to determine in any given patient whether or no he will have another hemorrhage, or how soon there will be a recurrence of hemorrhage. Neither is a physician able to tell in any given case the consequences of hemorrhage—whether a long uncontrollable "spurter" will be opened, whether perforation will occur immediately or within a short time or whether the extension of the ulcer will involve to a dangerous degree an adjacent viscus. In the circumstances, it is only fair to any subject that the true condition be explained to him, and, provided the bleeding does not result from a blood dyscrasia, or during a physiologic cycle such as the menopause, or in association with a disease not definitely ascribable to the stomach or duode-

num, surgical exploration and treatment should be insisted upon. Frequently, such course of management is refused by the patient, but if the physician has made his viewpoint clear and the patient understands it and is willing to assume the risks, then the physician is relieved of much responsibility in the carrying out of any regime other than surgical. It is astonishing how frequently, however, both patient and physicians are ready to gamble upon the future, when the patient has already experienced one severe gastric or duodenal hemorrhage. While this may be human nature, yet when crises occur, the patient who is turned over for surgical management is in a far more hazardous state than he would have been had surgical intervention occurred at a time when the patient's general condition was excellent and what had to be done surgically could have been carried forward in a leisurely and scientific manner.

*The stoppage of bleeding by drugs* has not, in my experience, been very successful. This is probably due to the fact that I have not employed many drugs for such purpose but rather, by keeping the patient at rest in bed, stopping peristalsis by morphia, supplying sufficient fluid to stimulate cerebral activity and keeping the stomach free from food, etc., I have not had to employ many of the commonly administered local hemostatics. Not rarely, one hears of good results following the introduction into the stomach of such mixtures as adrenalized gelatin, adrenalin solutions, tannic acid solutions, etc., etc. The use of adrenalin intramuscularly or the in-

tramuscular administration by the hypodermatic route of coagulating agents such as thrombo-plastin, coagulose, horse serum, etc., has been favorably recommended. Certainly, if these agents are not administered in such quantities as to produce harm, one may employ them on the general theory that they may do good, or that, if the case should turn out badly, these agents having been administered, the physician's conscience is clear, inasmuch as he has exhibited all known remedies to prevent a catastrophe. However, no one yet has shown just how much of the above agents it is necessary to give to any individual or to any group of individuals, in order to stop gastric or duodenal bleeding, whether that bleeding be due to seepage or to free bleeding from an arteriole or an artery. Further, I have always felt that the administration of the above mentioned agents leads to a sense of false security, and that while these agents were being pumped into the patient, bleeding was progressing to the point where serious loss of blood might take place or the continued bleeding extend such lesion as an ulcer to the stage of fatal perforation. In my experience, the most potent agents to stop bleeding when the bleeding was not from a "spurter" have been the intravenous administration of 20 c.c. of five per cent calcium chloride solution every two hours for six doses, or, better still, prompt transfusion of large volumes of whole blood after the method of Kimpton, Brown-Percy. If these agents do not stop bleeding within thirty-six to forty-eight hours, it is evident that one has to do with a condition where it would

be wise to urge surgical exploration without delay. Such exploration may reveal a bleeding malignant ulcer, an arteriole dripping constantly, or an artery from which an obstructing blood clot is frequently dislodged.

It has been advanced by individuals, quite carelessly and without clinical or laboratory proof, that blood transfusion tends to prolong hemorrhage by increasing blood pressure or by dislodging clots from the mouths of arterioles or arteries or by both. In a rather extensive clinical experience, I have never seen any ill effects following the massive transfusion of whole blood; but I have seen instances where neither blood transfusion nor any other measure permits the formation of an obstructive clot at the mouth of a "spurter" of fair size. The opinions which have been advanced regarding how much massive whole blood transfusion (and I speak of "whole blood" transfusion because it has never been our policy to use citrated blood or blood altered in any other manner) increases blood pressure or dislodges clots, have been repeated by one clinician after another, without there seeming to have been, so far as I can learn, any basis of fact for these opinions. In order to learn definitely just what effect increase in blood volume or increase in blood pressure has upon a freely bleeding vessel, at my suggestion, my associate, Dr. Ralph A. Kordenat, carried forward a series of experiments which he will report in detail later, but from which he has permitted me to make certain statements. Working with fairly large dogs at the Research Laboratories of the Univer-

sity of Illinois, Dr. Kordenat and his associates exposed arterioles and arteries, severed them and permitted free bleeding and subsequent clot formation at the mouths of the vessels. The intravenous introduction of fluid in quantity almost to "water-log" the dog did not dislodge the clot, nor did the hemorrhage recur when the blood pressure had been raised, mechanically or by the use of adrenalin, to more than double the normal blood pressure. Furthermore, quantities of fluid, intravenously introduced and comparable in proportion to body weight or to the animal's normal fluid content, added to such amounts of blood as would be introduced during a therapeutic transfusion, resulted in but a very slight and transient rise in blood pressure, and had no effect whatever with respect to producing a recurrence of hemorrhage. These experiments, conducted by Dr. Kordenat and his associates, would seem to be of the greatest importance in demonstrating the harmlessness of whole blood transfusion as therapeutically carried out in the control of visceral hemorrhage, and should be of great assurance to physicians in their proceeding to transfuse promptly and frequently individuals whose visceral hemorrhages are not controlled by general and visceral rest. These experiments substantiate completely our clinical experience with regard to therapeutic transfusion of whole blood, and also the intravenous exhibition of saline solutions and calcium chloride.

*Persistence of visceral bleeding usually indicates pathology that war-*



rants surgical exploration. Too often, patients are permitted to die from exhaustion, shock or anemia, because bleeding is allowed to continue interruptedly, while futile efforts, therapeutically or dietetically, are being made to stop hemorrhage, nourish a patient or "build up the blood." As I mentioned above, should an increasing pulse rate, a falling blood pressure and a falling blood count and hemoglobin estimation continue, the patient should be explored by a competent surgeon while he still is a fair surgical risk. Not infrequently, a persistently bleeding ulcer can be excised or enfolded, a "spurter" ligated or a small malignant ulcer excised, largely under local anaesthesia, and within a few days the patient is past danger and has a fairly reliable future ahead of him. Furthermore, this prompt action not rarely prevents perforation and fatal hemorrhage or peritonitis.

Thus far, I have not mentioned the use of the *x-ray* as an aid in determining the pathology responsible for gastrorrhagia. Purposely I have not mentioned the *x-ray*, hoping that it would be self-evident that *x-ray* investigation had little place in the locating of pathology productive of gastrorrhagia. Certainly, in acute hemorrhage or in persistent seepage, one should endeavor to forget that the *x-ray* method of investigating the alimentary tract had ever been devised. Every year it has been my misfortune to observe individuals who have ex-

perienced acute gastric hemorrhage and upon whom, even while bleeding persisted, the *x-ray* method of investigation has been employed. In many of these patients, the heavy barium mixtures have not only prolonged hemorrhages and made them more severe, but in numerous instances the consequences have been fatal on account of resultant perforation. It is our policy never to *x-ray* a patient by means of barium mixtures until at least four weeks following proof of cessation of a severe hemorrhage. Even then, one should proceed cautiously with both the fluoroscopic and the plate studies. Certainly, the use of the *x-ray* method while a patient is still bleeding subjects the individual to hazards which no roentgenologist or clinician should be willing or anxious to assume. For the guidance of house officers in all hospitals, there should be displayed prominently cautions that individuals who are brought into the institutions during gastrorrhagia or in whom gastrorrhagia appears, should not be *x-rayed* without the written permission of their chiefs. If, from clinical history, physical examination and the various simple laboratory tests which have been outlined above, a workable appraisal of the condition to be treated cannot be made, certainly, little of value will be added to the picture by roentgen studies, and most assuredly the patient will be subjected to risks out of all proportion to any information which may be gained.

# Experiments With Phenylhydrazine

## I. Studies On the Blood\*

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and

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SINCE 1918, when Eppinger and Kloss (1) first introduced phenylhydrazine in the treatment of polycythemia vera, an increasing number of reports from the clinical standpoint have been recorded, notably those of Owen (2) and Brown and Giffin (3). Notwithstanding the excellence of these reports, certain fundamental questions in connection with the effect of the drug remain unanswered. This is due to the difficulty of keeping in touch with patients over long periods and more particularly to the impossibility of subjecting them to the rigid research methods which can be conveniently carried out on animals.

The experimental work on animals has so far been directed largely toward the study of the effect of phenylhydrazine on the erythrocytes, and the chemistry of the blood. The effect of hydrazine compounds other than phenylhydrazine has been noted in experimental work on the liver. Investigations of the effect on other vital structures, particularly the kidneys, bone marrow and spleen, have been negligible as have studies on the effect of

the total and differential leukocyte count. Moreover, too much attention has been paid to the toxic effects and pathologic changes due to phenylhydrazine and allied compounds, and far too little to the dosage used to produce these changes. Wells (4) has been widely quoted as having demonstrated fatty degeneration of the central cells of the hepatic lobule, but he used 0.1 gm. of hydrazine sulphate (not phenylhydrazine hydrochloride) for each kilogram of body weight in a single dose, an enormous amount as compared with the therapeutic dosage of phenylhydrazine. Other hydrazine compounds have been more extensively studied than phenylhydrazine itself, and conclusions with regard to the

†Bibliography for Studies I and II given at the end of Study II.

\*Abstracted for Proceedings of the Staff Meetings of the Mayo Clinic, 1927, ii, 154-156.

The material in this paper was presented in a thesis by Edgar V. Allen to the Faculty of Minnesota in partial fulfillment of duty of the Graduate School of the University of the requirements for the degree of M.S. in Medicine, 1928.

toxicity of phenylhydrazine have been drawn from these studies. That this is unjustified is evidenced by the fact that these compounds have diverse effects; for example, the absence of erythroclastic action after the administration of hydrazine sulphate.

In this study we have regarded compounds allied to phenylhydrazine as foreign to our problem and have limited investigation to the effects of phenylhydrazine administered in a manner comparable to its use clinically. Dogs have proved to be excellent animals for this purpose. The amount of the drug given to these animals in a period of five months of active treatment is equal to that given clinically in a period of from four to six years. This has permitted us, in a comparatively short time, to study the effects of experiments that would otherwise be prolonged. The specific information sought in these experiments is as follows:

The general effects of prolonged administration.

The effect on the erythrocytes of large but sublethal doses.

The effect on the total number of leukocytes and on the differential proportion.

The determination of dosage.

The effect of the drug on the splenectomized animal.

The effect on the erythropoietic function.

The effect on renal and hepatic function.

Pathologic changes after prolonged administration.

#### METHODS OF STUDY

Healthy full-grown mongrel dogs weighing between 4 and 12 kg. were used. An unlimited amount of dog biscuit, adequate for normal dogs, was their constant diet. The phenylhydrazine was given subcutaneously in an aqueous solution or by stomach tube. Bromsulphalein and phenolsulphonaphthalein were used in the estimation of hepatic and renal function, respectively. Blood was obtained directly by ear puncture for the enumeration of erythrocytes, leukocytes and the differential count; 200 cells were counted (in the future we expect to count 500 cells). Hydrochloride of phenylhydrazine was used, and the dosage was calculated from the body weight.

#### GENERAL EFFECTS

No untoward general symptoms were noted in the dogs given doses approximating those used clinically, during the experiments. Thrombosis of the superficial veins, a frequent complication in polycythemia vera, was not noted. Vomiting occurred in a few instances after the administration of the drug by stomach tube, but this was rare. Subcutaneous injections were attended by some discomfort. The dogs did not gain or lose weight excessively, and they appeared to be well throughout the experiments. Augmented toxicity was not observed when the drug was given subcutaneously. Early in these experiments we were convinced of the equivalent action of the drug when it was given subcutaneously and by mouth. Recently Long has demonstrated that intraperitoneal administra-

tion is effective. The total dosage given to three animals was comparatively enormous; the dose for one was 1.26 gm. for each kilogram of body weight and for the other two only a little less. This would be equivalent to 88 gm. for a man weighing 70 kg. and enough to treat the average case of polycythemia vera for from four to six years. That the animals were well after being given these large amounts is evidence of the lack of toxicity of the phenylhydrazine hydrochloride in therapeutic doses.

#### EXPERIMENT 1. THE EFFECT OF A LARGE AMOUNT OF PHENYLHYDRAZINE

Four animals were selected for the study of the comparative effects of various doses on the general condition and on the number of erythrocytes. All four dogs were given, by stomach tube, a total of 60 mg. of phenylhydrazine for each kilogram of body weight. The first dog was given the full amount in a single dose on the first day of the experiment, the second dog was given the full amount in two equal doses on the first and second days, the third dog was given the full amount in three equal doses on the first, second and third days, and the fourth dog the full amount in ten equal doses on each of the ten days of the experiment. (fig. 1.) The reduction in the number of erythrocytes was almost equal in the four dogs at the end of the experiment. In the first dog erythrocytes were markedly reduced between the first and third days after which the reduction was more gradual until the eighth day when there was a slight increase. In the

second dog the erythrocytes were markedly reduced between the fourth and sixth days. Between the first and fourth days the reduction was more gradual and there was an increase after the sixth day. In the third dog the reduction was more gradual although it was marked between the sixth and seventh days and was followed by some regeneration between the seventh and tenth days. In the fourth dog there was a uniform reduction from the first to the tenth day. From this experiment it seems reasonable to conclude that a reduction dose of phenylhydrazine will cause approximately equal reduction in erythrocytes at the end of a ten-day period whether it is given in a single dose or in divided doses. The rate of reduction, however, is variable, being maximal in the animals given single doses and minimal in the animals given the greatest number of doses. The latter method of administration is most desirable because of the gradual effect but the former can be used without apparent harm. This information has been of value in clinical experience and we have been able to shorten the refractory period (between the time the drug is first administered and the appearance of evidence of reduction) by increasing the dosage the first two or three days of treatment.

#### EXPERIMENT 2. THE EFFECT ON THE ABSOLUTE NUMBER OF THE LEUKOCYTES

*The leukocytes.*—An increase in the number of leukocytes has been noted clinically by Owen, Brown and Giffin and by Altnow and Carey (5). Leo-

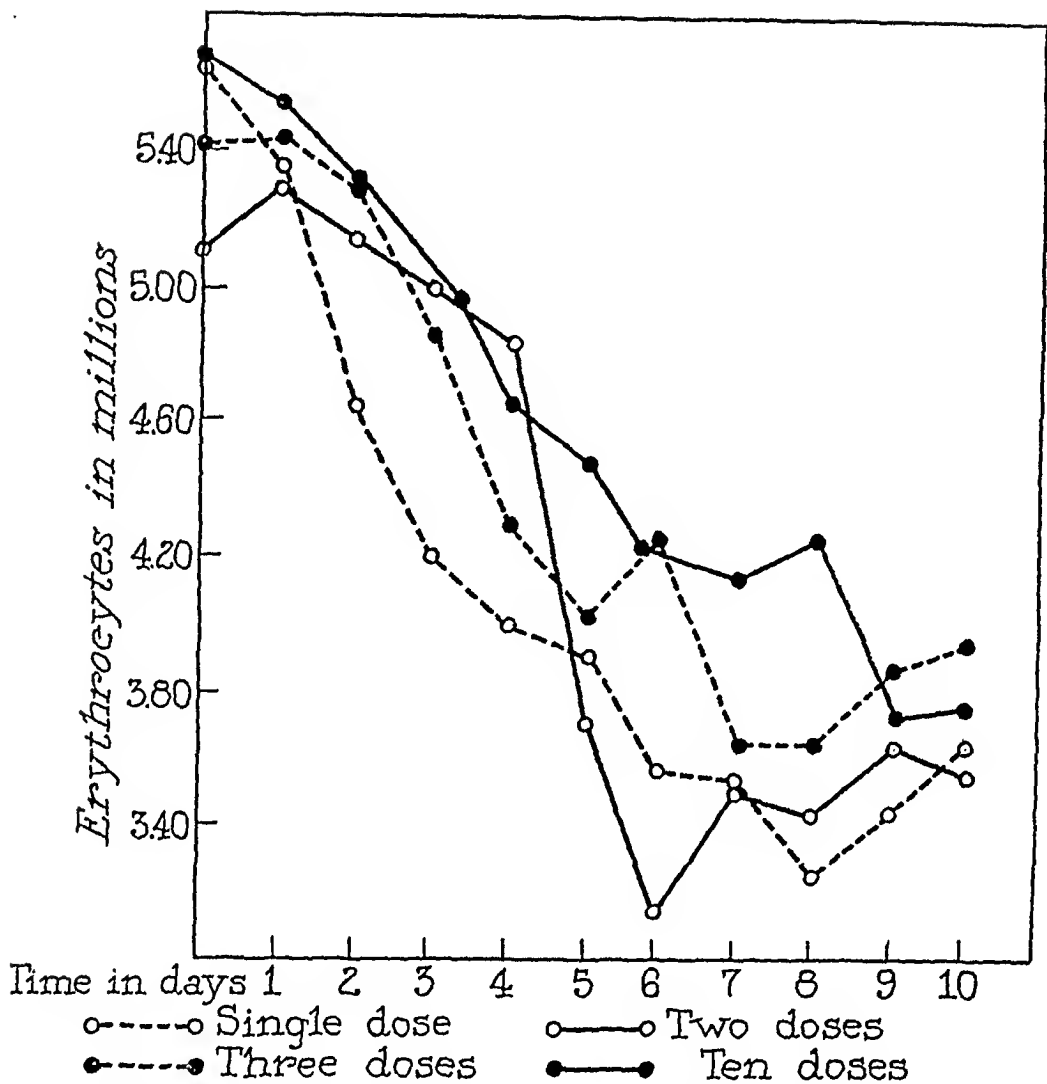


FIG. 1. The effect on the erythrocytes of 60 mg. of phenylhydrazine for each kilogram of body weight in single and divided doses.

pold (6) found no change clinically, and Long (7) could not demonstrate an increase in rabbits. Owen believed the number of leukocytes might indicate the rate of destruction of erythrocytes and that "the occurrence of a leukocytosis is a highly important index in controlling treatment." Our clinical experience has not supported this. Changes in the number of leukocytes in these experiments following the administration of phenylhydrazine were not constant. Thus there was an

increase in the number of leukocytes following the administration of phenylhydrazine in ten experiments. (figs. 2, 3, 4, 5, 6 and 7, *d, e, f, g, h*, and no increase or a slight reduction in four experiments (figs. 7, *a, b, c*, and 8). Theoretically the factors which might influence this variation are the amount of the drug, the period over which it was given, the method of administration, and previous administration. The methods of administration and previous adminis-

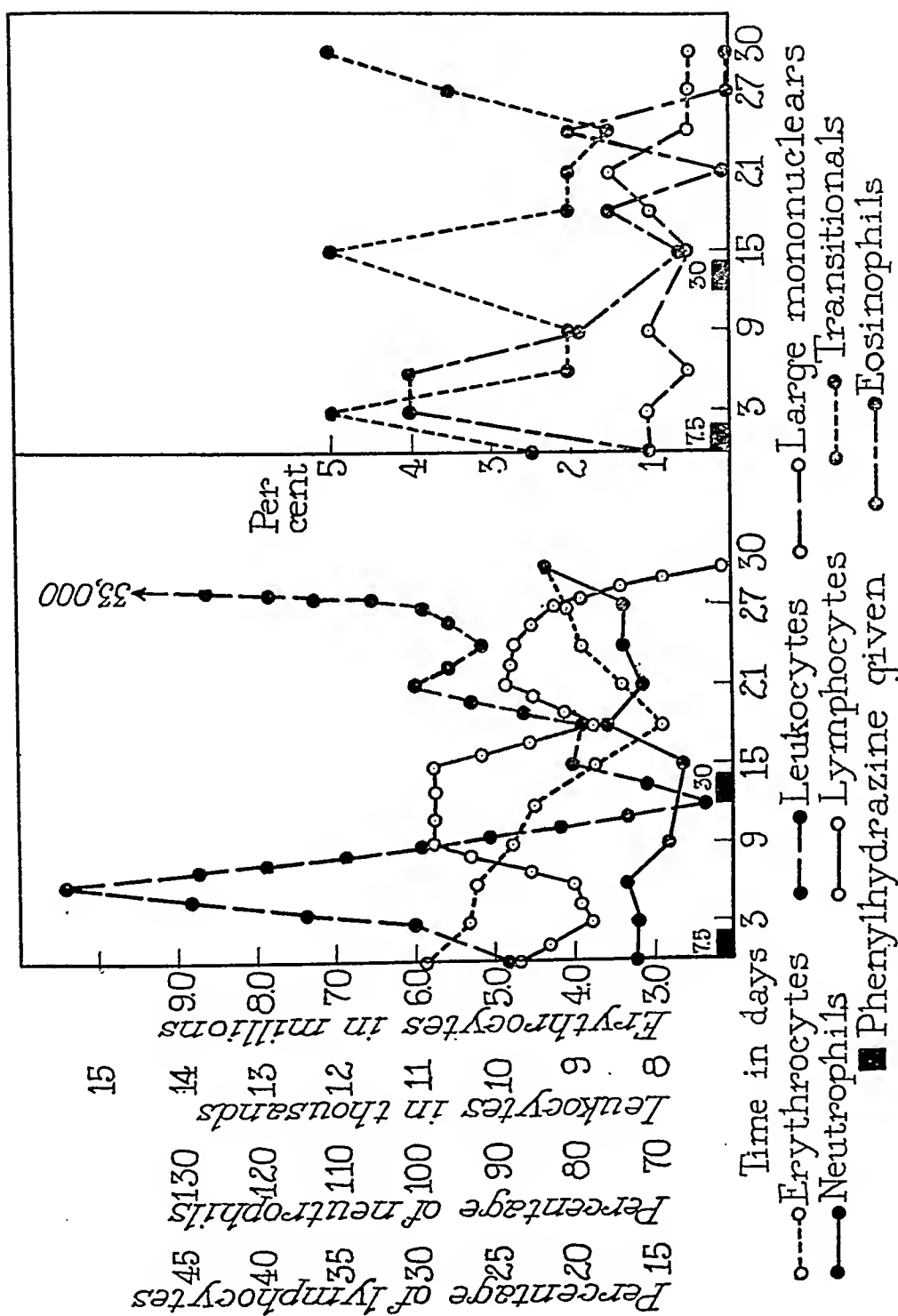
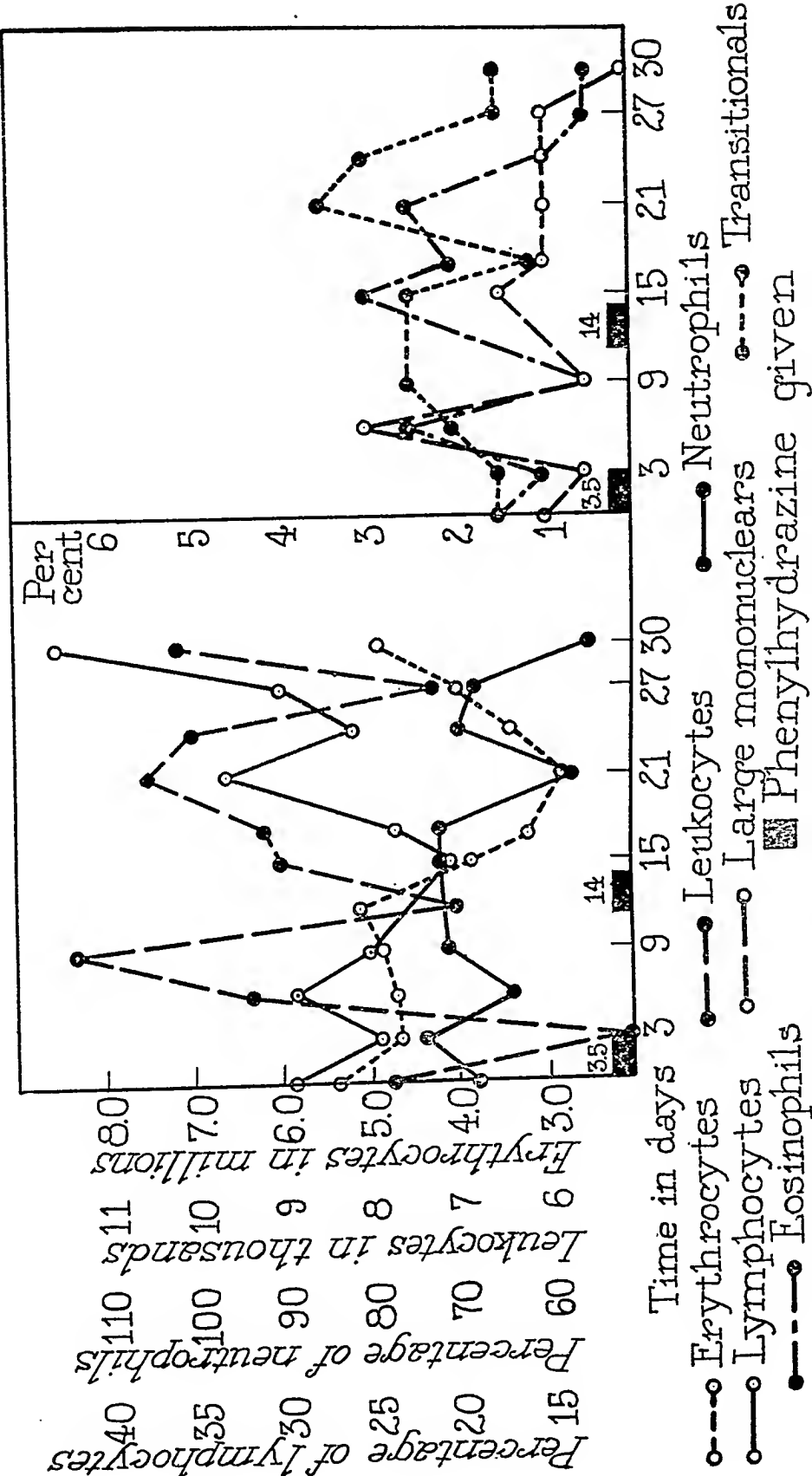


FIG. 2. The effect of experimentally administered phenylhydrazine on the number of leukocytes and the differential count. (In this and the following figures the numeral on the block representing the time of the administration of phenylhydrazine indicates the milligrams of phenylhydrazine for each kilogram of body weight.)



FIGS. 3, 4, 5, and 6. The effect of experimentally administered phenylhydrazine on the number of leukocytes and the differential count.

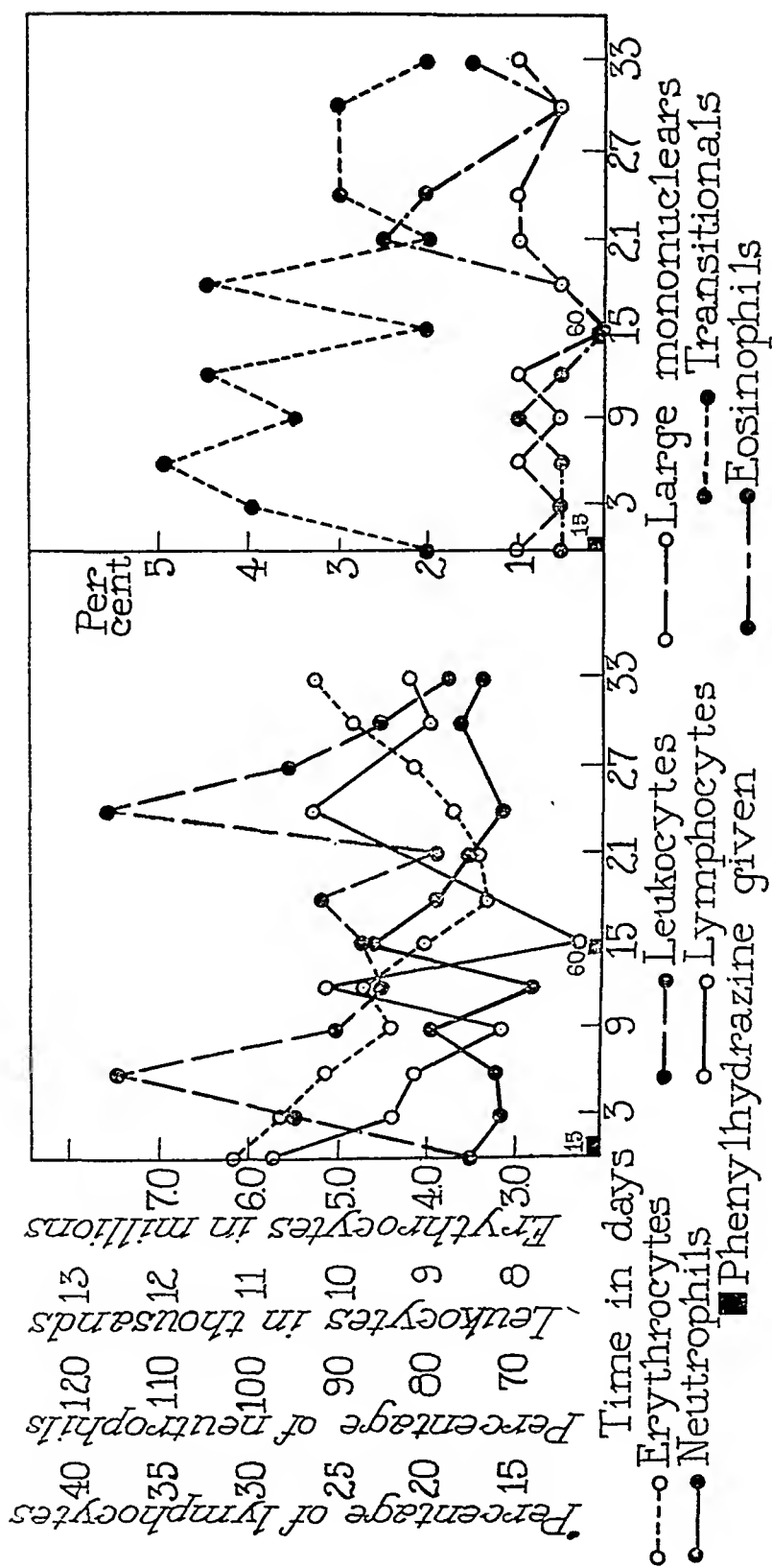


FIGURE 4



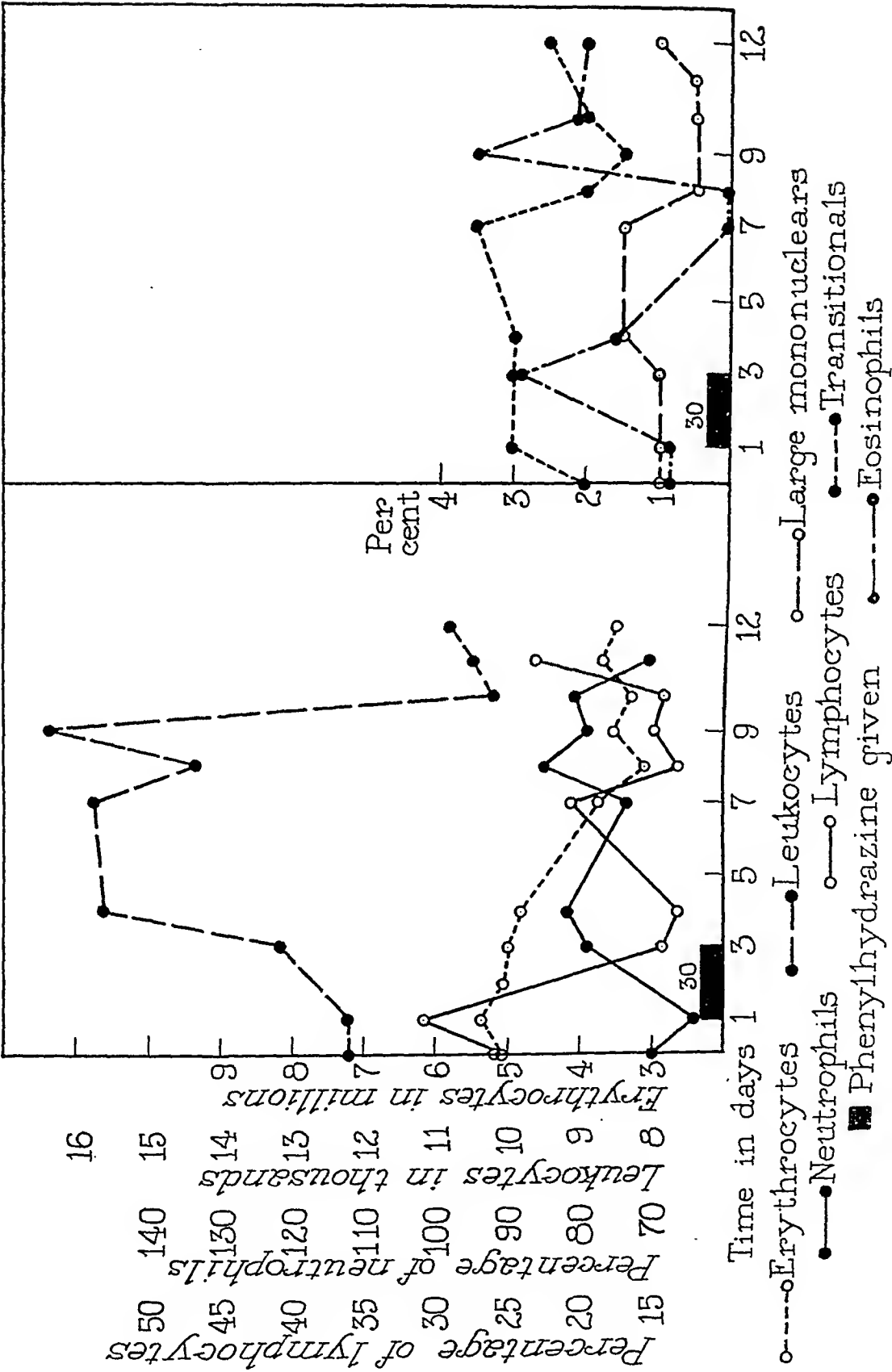


FIGURE 5

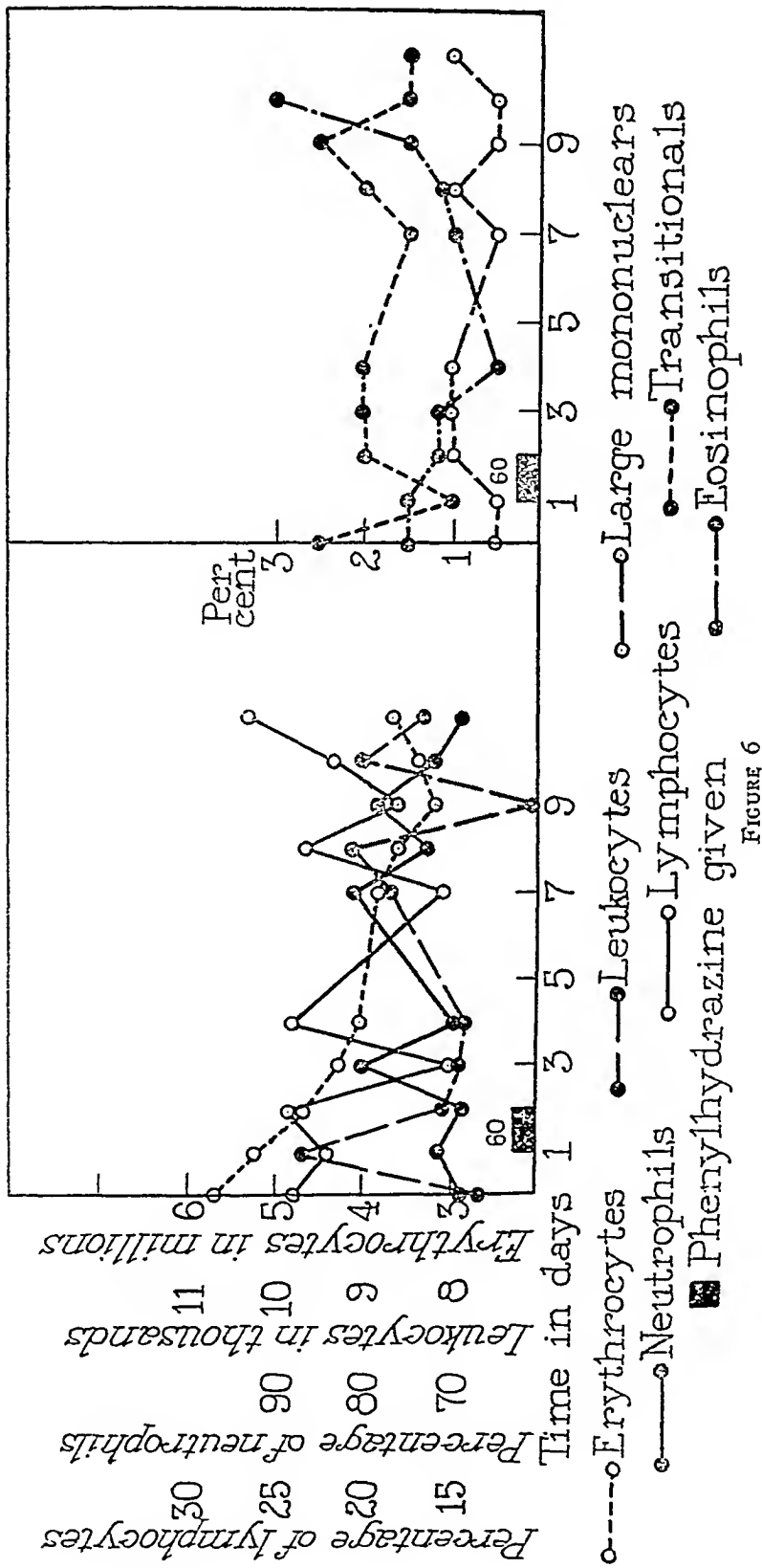


FIGURE 6

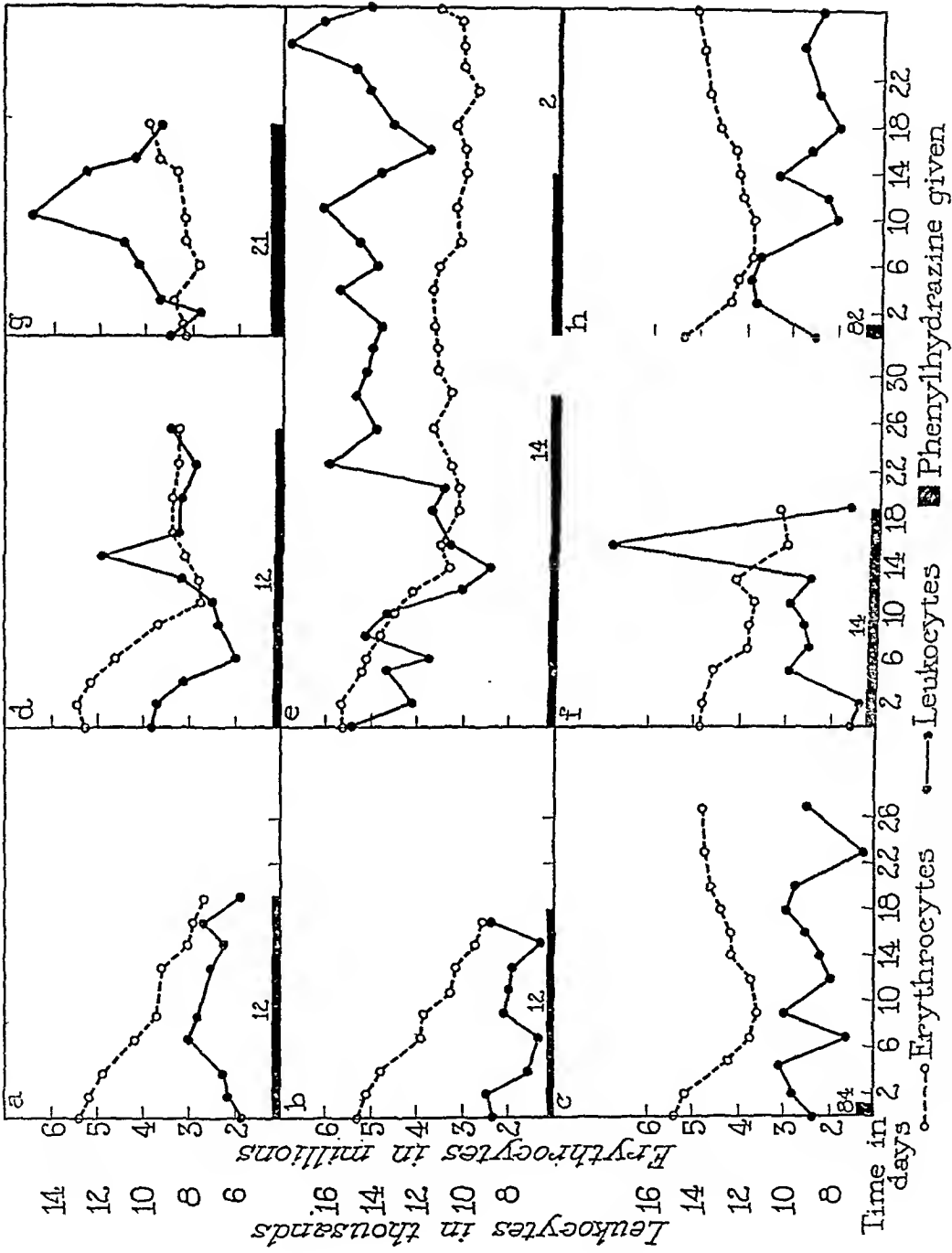


FIG. 7. The result of experimentally administered phenylhydrazine on the number of erythrocytes and leukocytes. The results of eight separate experiments are shown.

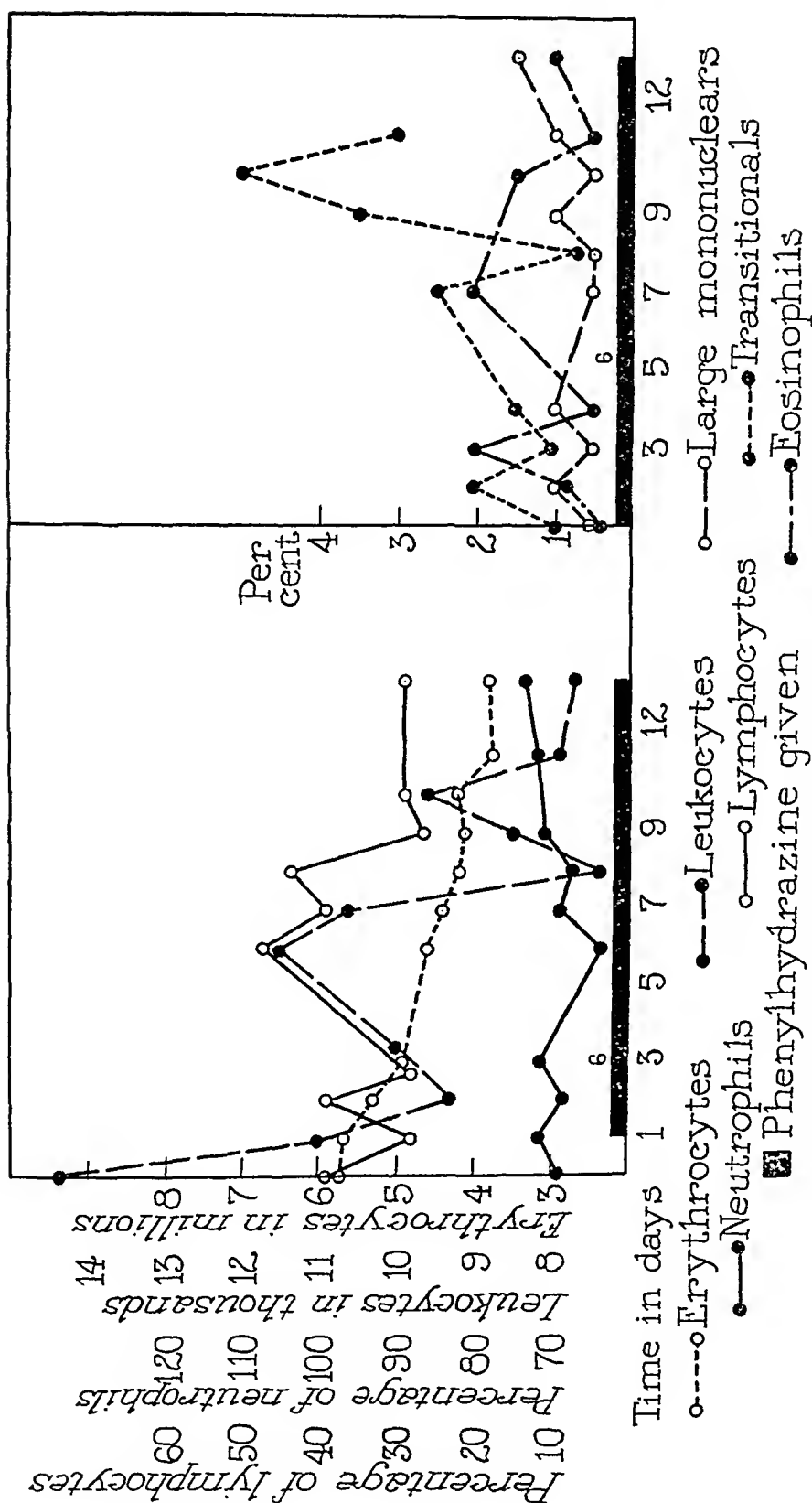


FIG. 8. The effect of experimentally administered phenylhydrazine on the number of leukocytes and the differential count.

tration apparently were not factors. The most frequent and the most marked increases in the number of leukocytes were found in animals given rather large amounts of the drug on one or two days. The outstanding exception is shown in figure 7c; there was very little response after the administration of 48 mg. of phenylhydrazine for each kilogram of body weight. Appreciable increases were noted in two animals (fig. 7 e, g,) which were given phenylhydrazine daily.

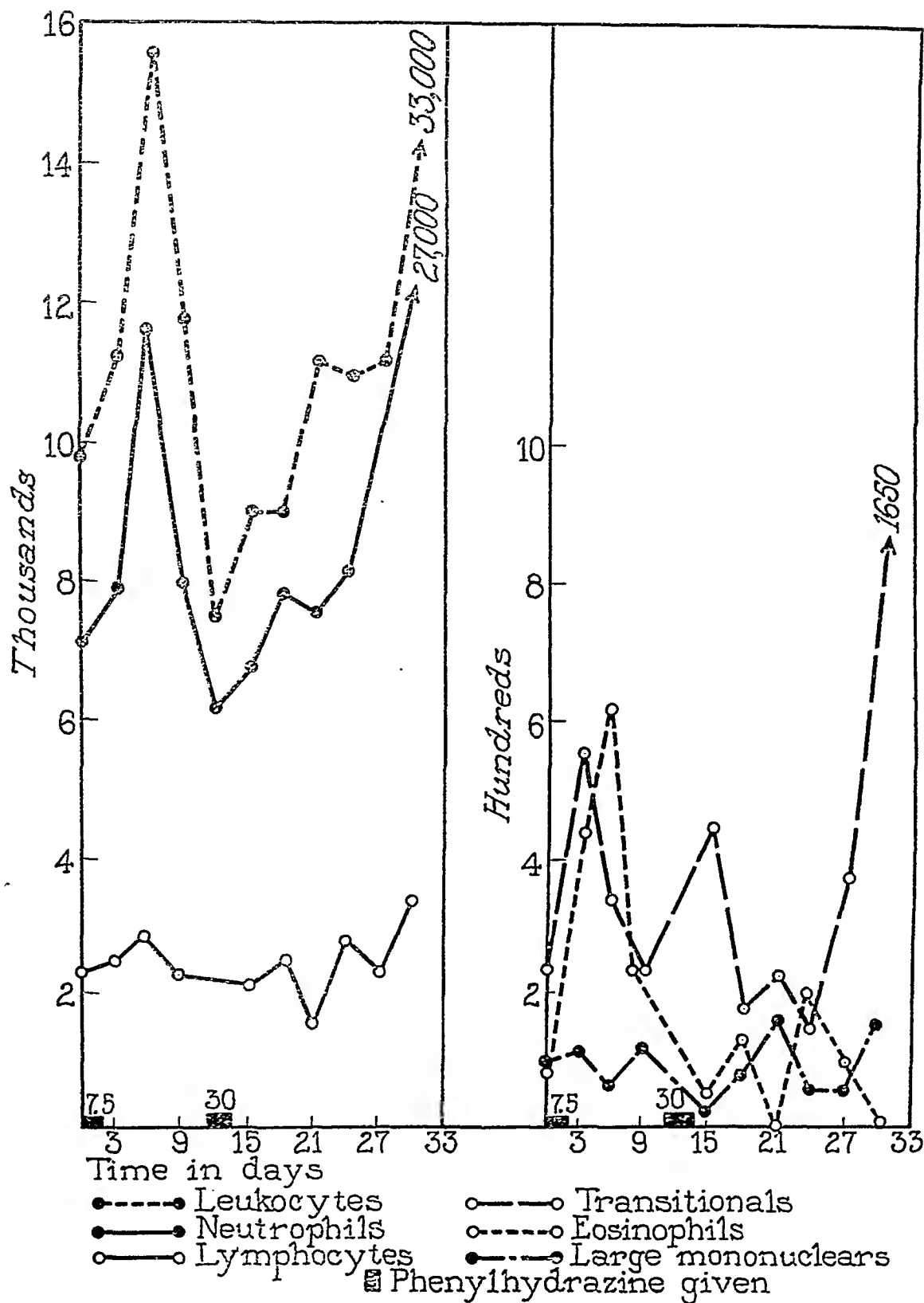
The cause of the leukocytosis has been debated. Owen's work led him to believe that the leukocytosis was secondary, and probably the result of tissue destruction rather than stimulation of the bone marrow. Brown and Giffin believe that their clinical experience indicates that the drug exerts specific stimulation on the production of leukocytes, and Altnow and Carey conclude that there is a direct stimulating effect on the bone marrow. The results in our experiments were variable. In three instances (figs. 2, 3, and 4) there was apparently a specific response, which was independent of the effect on the erythrocytes, as the number of leukocytes increased soon after the drug was given and returned to a lower level after withdrawal of the drug at a time when the number of erythrocytes was decreasing rapidly. However, in four experiments (figs. 6 and 7 d, f, and h) the leukocytosis could well have occurred secondarily.

Our data, therefore, indicate an irregular response of the leukocytes with an increase in most instances

which was at least frequently due to the specific action of phenylhydrazine and was not a result of the destruction of erythrocytes or other tissues. Two factors might contribute to this irregularity of response: prolonged action of phenylhydrazine after withdrawal which indicates either storage or slow excretion, and destruction of erythrocytes which continues even when the number of erythrocytes in the peripheral blood is increasing. A consideration of these factors makes it impractical to conclude that the secondary effects of the drug are responsible for the leukocytosis, and it also modifies the assumption of a specific stimulating effect of the drug on the production of leukocytes, for proof is lacking of the absence of increased destruction of erythrocytes when the number is stationary or increasing. Instances in which the leukocytosis decreases or disappears immediately following the discontinuance of phenylhydrazine offer evidence of a specific stimulating action.

*The neutrophils.*—The results of four experiments (figs. 9, 10, 11 and 12) during which the number of leukocytes was markedly increased, were used for the calculation of the absolute number of neutrophils, lymphocytes, eosinophils, transitionals and mononuclear cells. In each of these experiments there was almost an exact parallelism between the total number of leukocytes and the total number of neutrophils.

*The lymphocytes.*—The lymphocytes showed a somewhat more variable response than the neutrophils. In four instances there was, however, a rough



FIGS. 9, 10, 11, and 12. The effect of experimentally administered phenylhydrazine on the absolute number of leukocytes.

parallelism between the absolute number of leukocytes and lymphocytes, an increase or decrease in one being associated with the same change in the other (figs. 9, 10, and 11, second ad-

very little change in the total number of lymphocytes associated with definite increases in leukocytes.

*The transitionals.*—The absolute

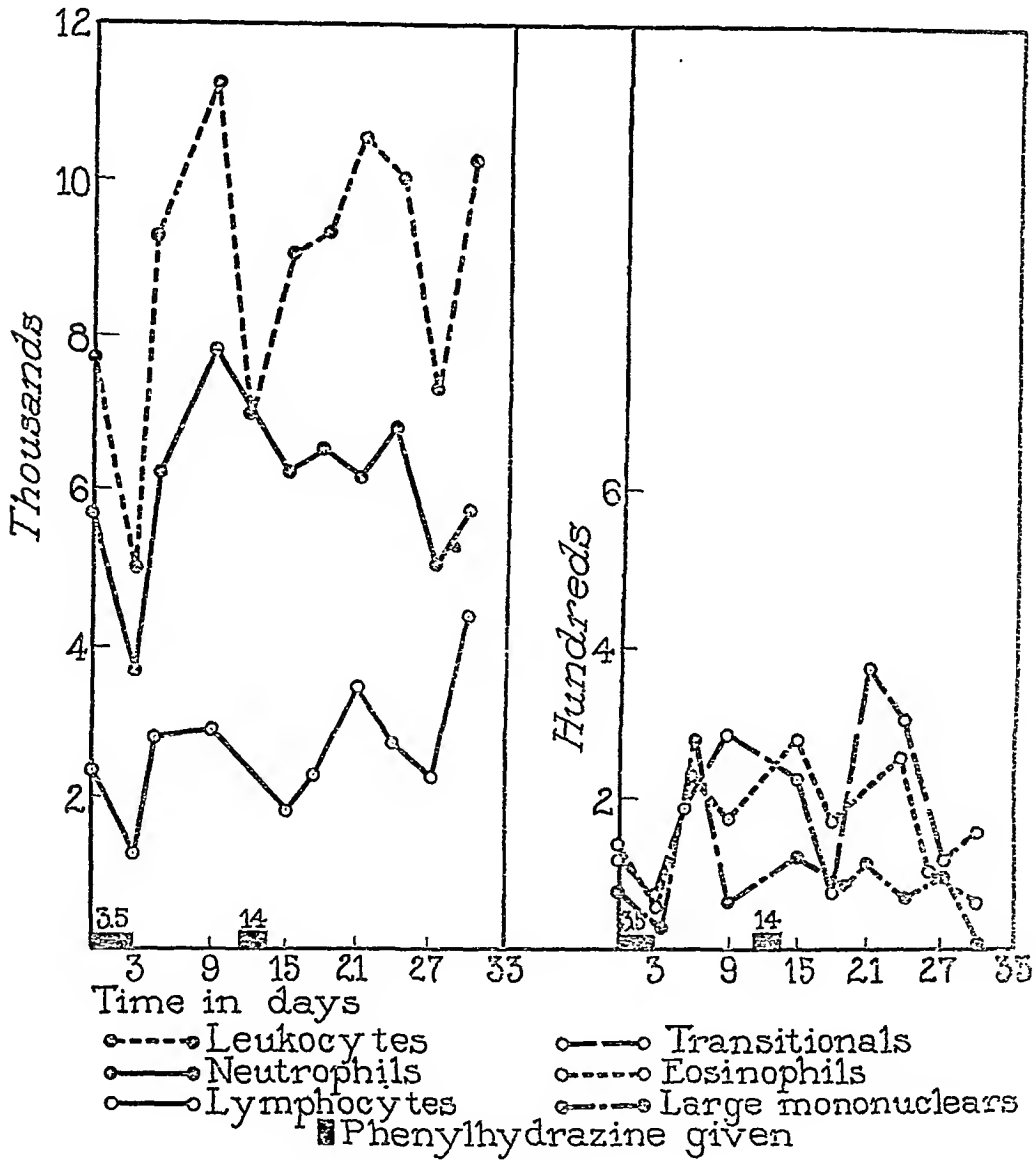


FIGURE 10

ministration, and fig. 12, after the seventh day). In figure 11 there was a decrease of lymphocytes (third day) followed by an increase which was associated with an increase of leukocytes. In two experiments (figs. 9, and 11, first administration) there was

number of transitional cells ran nearly parallel to the absolute number of leukocytes and was almost always well above normal. In one instance the remarkable number of 1650 transitionals was found; this, however, was only on one day.

*The eosinophils.* — The absolute number of eosinophils was variable. An increase in the number of leukocytes was associated with a similar

number of leukocytes was associated with an increase in the number of eosinophils in one instance (fig. 12, tenth day).

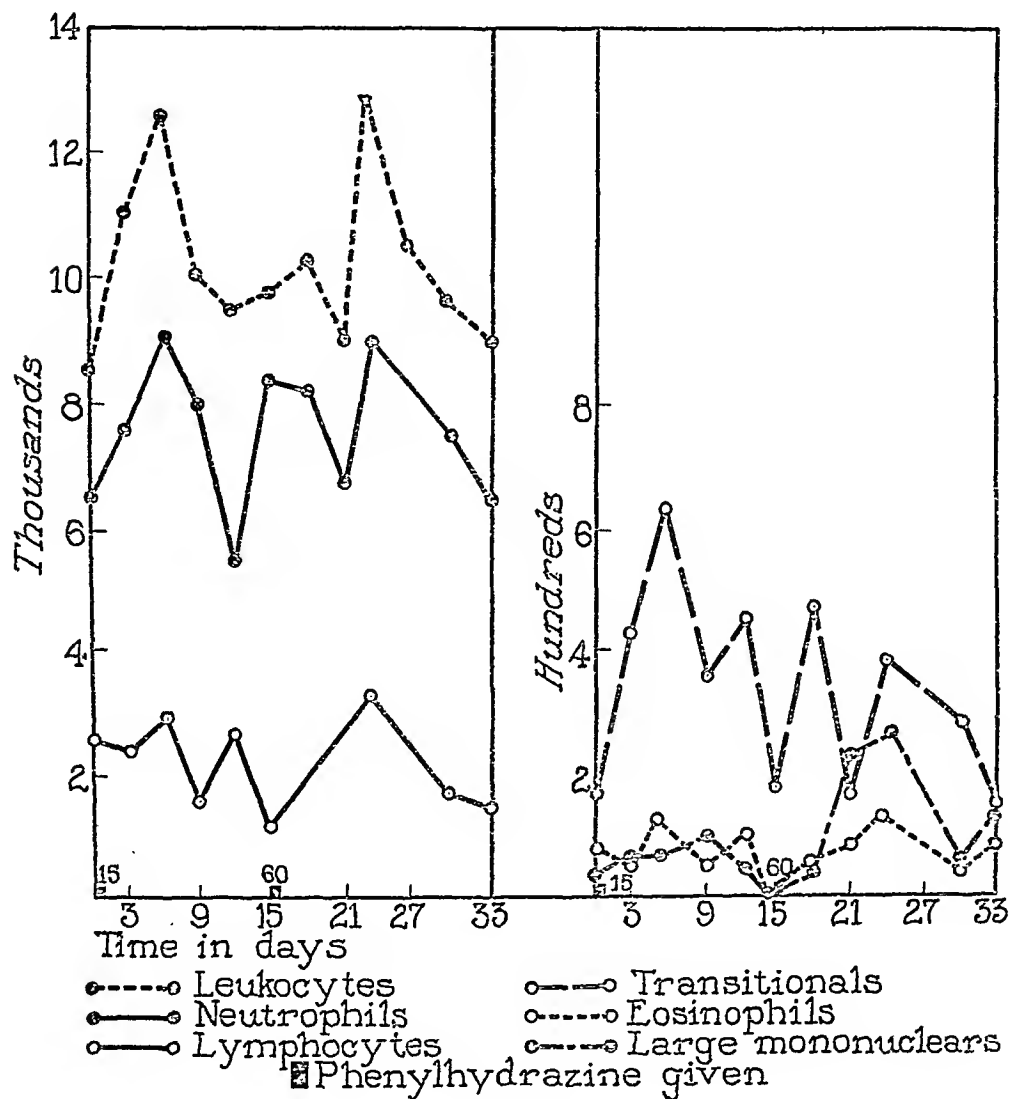


FIGURE 11

change in the absolute number of eosinophils in three instances (fig. 9, fifth day, and fig. 10, ninth and twenty-first days), a decrease in two instances (fig. 12 seventh day and fig. 10, thirtieth day) and no change in two instances (fig. 9 twenty-seventh day, and fig. 11). A decrease in the

*The mononuclears.*—Increases in the number of leukocytes were associated with a definite increase in the total number of large mononuclear cells in three instances (fig. 9, twenty-first day, fig. 11, twenty-fourth day, and fig. 12, fourth day), but with a decrease in one instance (fig.



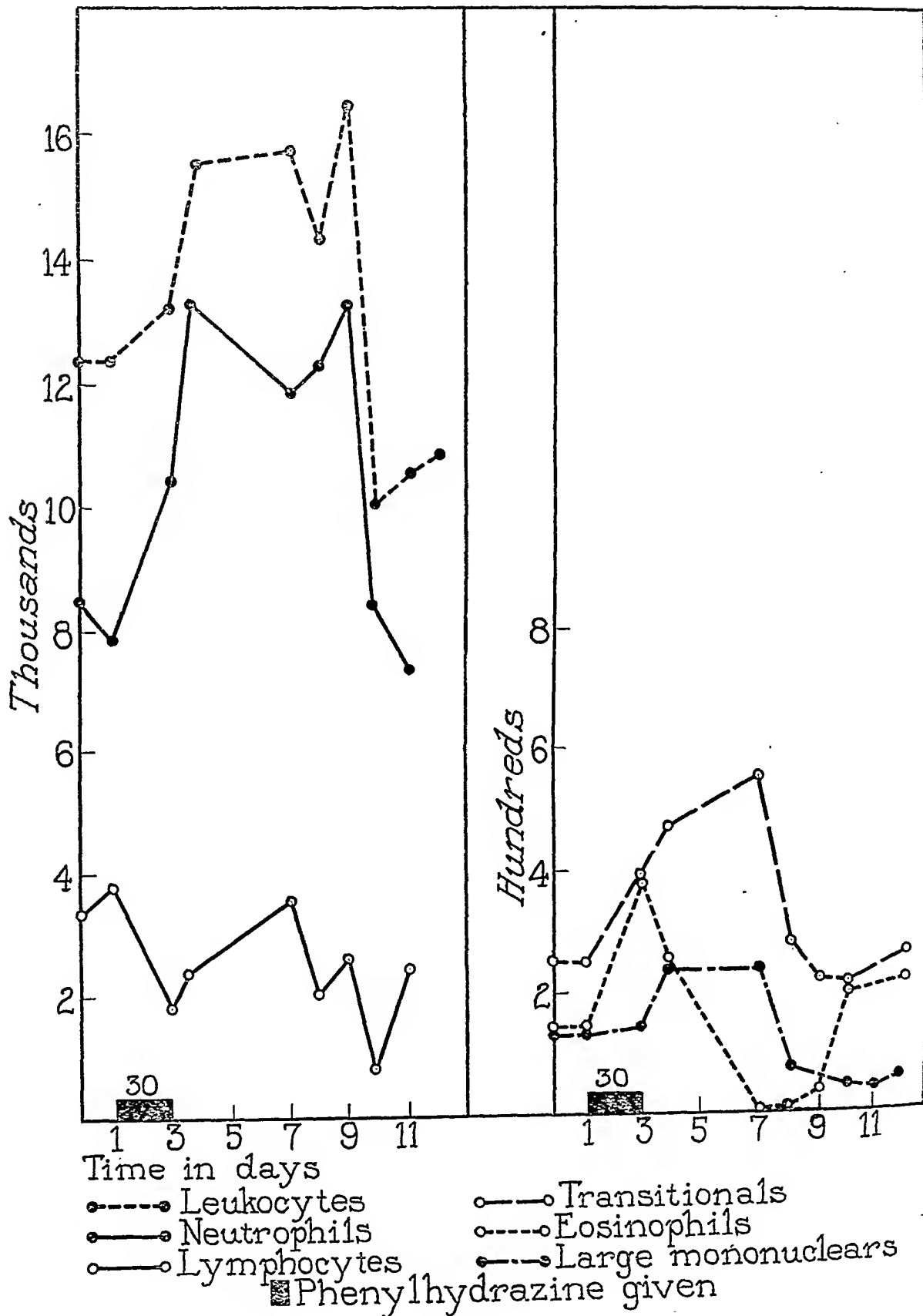


FIGURE 12

9, twenty-seventh day) and very little change in four instances (figs. 9 and 11, sixth day, fig. 10, ninth and twenty-first day). All of these changes were very small.

*Comment on Experiment 2.*—These data indicate a somewhat irregular response in the absolute number of neutrophils, lymphocytes, eosinophils, transitionals and mononuclears with, in most instances, parallel changes in the numbers of these cells when compared with changes in the total number of leukocytes. The neutrophils and transitionals showed the greatest increases.

### EXPERIMENT 3. THE EFFECT ON THE DIFFERENTIAL PERCENTAGE OF LEUKOCYTES

*The neutrophils.*—In four experiments (figs. 2, second administration, 4, 5, and 6) there was an increase in the percentage of neutrophils. In all of these cases there had been an increase in the total number of leukocytes. The increase in the percentage of neutrophils in each of these cases was roughly in proportion to the decrease in the percentage of lymphocytes. In one animal (fig. 3) there was a decrease in percentage of neutrophils associated with an increase in the total number of leukocytes. In two instances (figs. 2, first administration, and 8) there was no definite change in the percentage of neutrophils. In the first instance there was an increase in the total number of leukocytes and in the latter there was no increase. Although these data represent variable effects there is evidently a tendency to a relative increase of the percentage

of neutrophils, proportionate to a decrease in the lymphocytes.

*The lymphocytes.*—The change in the percentage of lymphocytes was extremely variable. There was definite increase in five animals (figs. 2, first administration, 3, second administration, 4, second administration, 6 and 8) but a decrease in the percentage of lymphocytes in four animals (figs. 2, second administration, 3, first administration, 4, first administration, and 5). Comparison of these changes with the changes in the percentage of neutrophils shows roughly a shifting mechanism between these two components, that is, a relative increase in neutrophils with a decrease in the lymphocytes, or vice versa.

*The transitionals.*—There was a definite increase in the percentage of transitional cells in all animals. (figs. 2, 3, 4, and 8) with one exception (fig. 6) in which there was little change. This increase was marked, in some cases increasing rapidly from a normal of 2 per cent to a high level of 5 per cent.

*The mononuclears.*—There was no change in the percentage of mononuclear cells (figs. 2, 4, 5, 6, and 8) with one exception (fig. 3) in which there was an increase.

*The eosinophils.*—Changes in the proportion of eosinophils were neither constant nor great. There was, however, a definite increase in several experiments (figs. 2, 4, 5, 6, and 8). In the experiment illustrated in figure 6 the increase occurred several days after phenylhydrazine had been discontinued and was probably not due

to the drug. In one instance (fig. 2, second administration) there was no significant change.

*The basophils.*—Basophilic cells are normally so few in the blood of dogs that there may be none in 200 leukocytes. These cells were carefully observed in the experiments, but no significant change was found.

*Comment on Experiment 3.*—These data on changes in the percentage of neutrophils, lymphocytes, eosinophils, mononuclears and transitionals indicate an irregular response. The most common observations were an increase in the percentage of neutrophils with a decrease in the percentage of lymphocytes; occasionally the reverse was true, increase in the percentage of transitional cells, slight change in mononuclears, and little change, usually slight increase, in the percentage of eosinophils.

Owen noted relative polymorphonuclear leukocytosis in a case of polycythemia vera treated with phenylhydrazine. Altnow and Carey studied one case in greater detail. They found that the absolute number of polymorphonuclear eosinophils and neutrophils increased and the number of lymphocytes and mononuclear cells did not change or were diminished. Hence they concluded that phenylhydrazine stimulated the bone marrow, but failed to stimulate or actually depressed the reticulo-endothelial system. These authors mention the incompleteness of their data as studies were not begun until the thirteenth day after treatment was begun and three days after the drug had been discontinued. Benzol and radium treatment had been given previously.

Our data are in accord with those of Altnow and Carey with respect to the usual increase of polymorphonuclear neutrophils and eosinophils but this increase did not always occur. In contrast to their data, however, the absolute number of lymphocytic, mononuclear and transitional cells frequently increased in our experiments. We did not find the increase in basophils noted by them. We could not detect stimulation of the production of any type of cell to the absolute exclusion of others.

#### EXPERIMENT 4. THE EFFECT OF DOSAGE

*Reduction dose.*—A reduction dose of phenylhydrazine is one which will cause definite and progressive diminution in the number of erythrocytes. The reduction of erythrocytes in response to a given amount of phenylhydrazine is fairly uniform, provided the period over which it is given is not too prolonged. This is shown (fig. 13) in the first two instances in which phenylhydrazine was given to cause a decrease in the number of erythrocytes in the three animals. In the first administration (fig. 13) Dog *a* received (over a period of three days beginning November 16, and three days beginning November 27) a total of 52 mg. for each kilogram of body weight, Dog *b* received (over a period of two days beginning November 16 and two days beginning November 28) 75 mg., and Dog *c* received (November 16 and November 29) 75 mg. The amount of destruction was almost equal in all cases. In the second administration (beginning December 25) each dog received 60 mg. for each kilogram of body weight with approximately equal

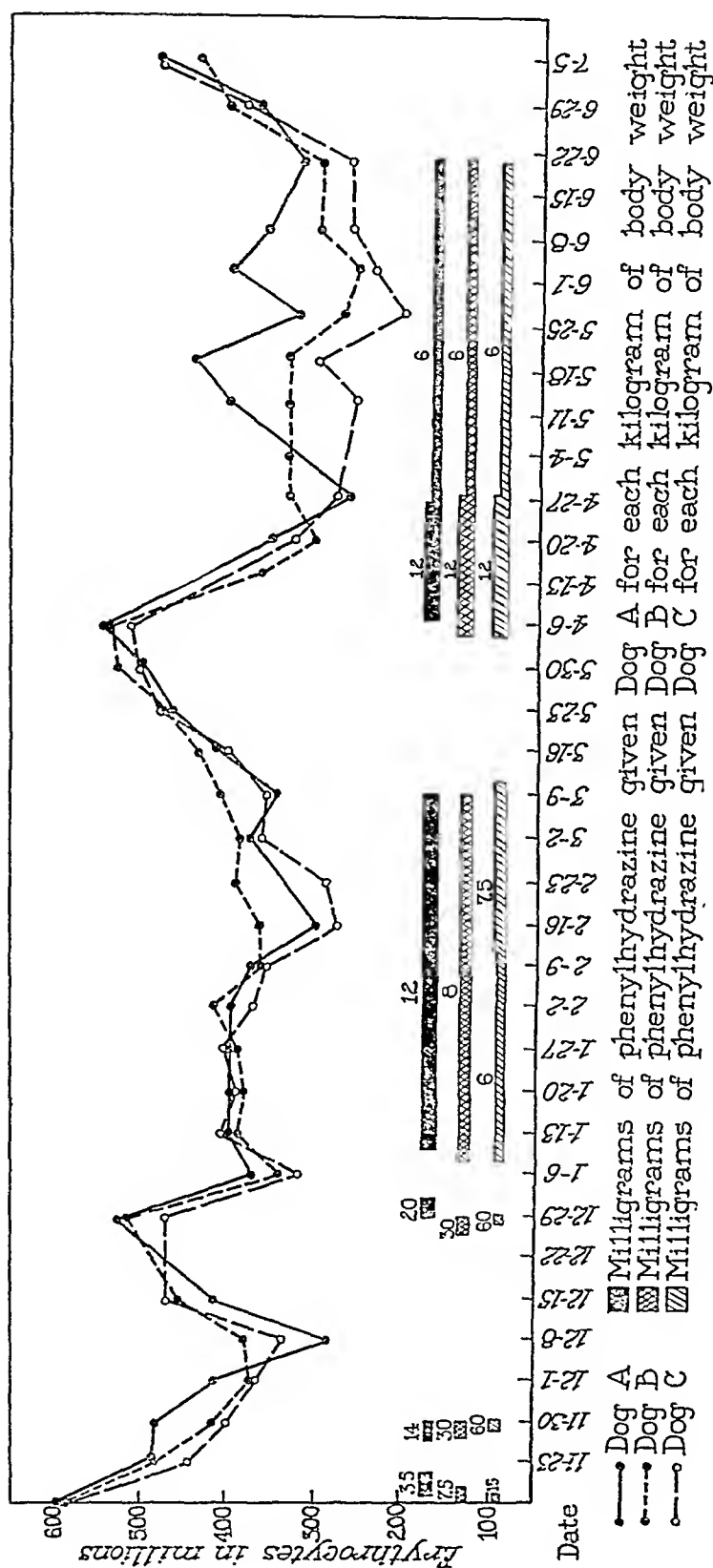


FIG. 13. The effect of experimentally administered phenylhydrazine on the number of erythrocytes. The references in the text to "first administration," "second administration," and "third administration" refer respectively to the inclusive dates November 16 to 30, December 24 to March 9, and April 6 to June 22. The effects on three animals are shown.

decreases in the number of erythrocytes. This uniform response to a certain amount of the drug is also demonstrated in all three animals in the third administration (fig. 13, April 6) as a result of 12 mg. for each kilogram of body weight, given daily. In calculating the decrease in erythrocytes for each milligram of phenylhydrazine for each kilogram of body weight, the amount of the drug given at each dose must be considered. Thus in the three animals (fig. 13, first administration) to which phenylhydrazine was administered over a period of one to three days the average dosage was 67 mg. for each kilogram, the average decrease in erythrocytes was 2,550,000 and the average decrease in erythrocytes for each milligram of phenylhydrazine for each kilogram of body weight was approximately 38,000 ( $2,550,000 \div 67$ ). Beginning April 6, smaller doses, given daily with an average dosage of 268 mg. for each kilogram of body weight, produced an average reduction in number of erythrocytes of 2,330,000, or roughly 9,000 for each milligram of phenylhydrazine for each kilogram of body weight. The latter method of administration more nearly parallels that used clinically. In the cases reported by Brown and Giffin the average weight was 65 kg., the average dose was 5.2 gm. and the average reduction of erythrocytes was 3,800,000. Calculated on this basis each milligram of phenylhydrazine for each kilogram of body weight caused a reduction of 47,500 erythrocytes for each millimeter. This number is high compared to that obtained in experimental animals, and the difference is probably explained by the greater

susceptibility of the erythrocytes in polycythemia vera.

*Maintenance dose.*—A maintenance dose of phenylhydrazine is one which will keep the number of erythrocytes at a more or less constant low level. It is apparent from many experiments that a reduction dose of phenylhydrazine within certain extremes, if given daily over a long period, becomes a maintenance dose and there is no further reduction in the number of erythrocytes. Examples of this are shown in figure 7 *d*, *e*, *f* and in figure 13 (Dog *a*). In the first instance 12 mg. for each kilogram of body weight was given daily and the reduction of erythrocytes was more than 2,000,000. On the eleventh day there was no further change and between the eleventh and twenty-sixth days there was a slight increase in erythrocytes. In the experiment illustrated in figure 7 *e*, 14 mg. for each kilogram of body weight was given for sixty-two days. There was active reduction of the number of erythrocytes until the fourteenth day, after which no change occurred. In the experiment illustrated in figure 7 *f* there was no change after the sixteenth day although phenylhydrazine was given daily. In figure 7 *a*, 12 mg. proved to be an active reduction dose, although given over a long period of time (fig. 13, Dog *a*) it did not cause the number of erythrocytes to go below 3,000,000.

There is a wide variability in the maintenance dose of phenylhydrazine. In two animals it was 14 mg. for each kilogram of body weight (fig. 7, *e*, *f*) while in one it was 12 mg. (fig. 13, Dog *a*, January 9); later (April 27) in the two animals (fig. 13, Dogs *b*

and *c*) 6 mg. for each kilogram of body weight was adequate. In the experiment illustrated in figure 7 *e*, 2 mg. was inadequate to keep the number of erythrocytes at a low level. Since it has been shown (in the description of reduction dosage) that phenylhydrazine has a direct quantitative action, the explanation of this variation probably lies in the fact that after a certain degree of anemia is obtained there is a compensating mechanism which causes new cells to be thrown into the circulation more rapidly. Thus, although 14 mg. for each kilogram of body weight given daily is a maintenance dose it is not a minimal maintenance dose; the minimal maintenance dose in dogs may be 6 mg. or less. Even this small amount is much greater than that which clinical experience has shown to be warranted in the treatment of patients with polycythemia vera. In fact this minimal maintenance dose in dogs is an adequate reduction dose in man. The explanation of this is not clear, but it is probably due to a greater susceptibility of the erythrocytes in polycythemia vera.

#### SUMMARY

Dogs given phenylhydrazine hydrochloride for 146 days in a period of eight months and a total dosage comparable to that of from four to six years of treatment of polycythemia vera in man, were well at the end of the experiments.

The drug had equal effects whether given subcutaneously or by stomach tube.

The same doses of phenylhydrazine produce approximately equal erythro-

clastic effects whether given in a single dose or in divided doses within a ten-day period.

Although the response is irregular there is a tendency toward an increase in the number of leukocytes, which in some instances is apparently due to specific action of the drug, and not to tissue destruction.

Although there was an irregular response in the absolute number of neutrophils, lymphocytes, eosinophils, transitionals and mononuclears there was in most instances a rough parallelism between changes in the numbers of these cells, and in the total leukocytes.

The transitional cells uniformly increased in percentage. The neutrophils increased in some instances and decreased in others. The percentage of lymphocytes varied in inverse proportion to the percentage of neutrophils. There was little change in the percentage of the mononuclear cells and eosinophils: in the latter there was a slight tendency toward increase. Basophils were so infrequently seen that they have been disregarded in this report.

Each milligram of phenylhydrazine for each kilogram of body weight caused a decrease of 38,000 erythrocytes when given in comparatively large doses within a three-day period, and as little as 9,000 when given over long periods in smaller doses. Clinically, in polycythemia vera a decrease of 47,500 cells has been demonstrated, a difference which is probably due to increased susceptibility of the red cells in polycythemia vera.

A reduction dose may become a maintenance dose if continued. The reason for this is not clear, but is prob-

ably explained by secondary stimulation of the bone marrow.

One must be exceedingly wary in drawing conclusions for clinical application from this experimental work. In the consideration of these data two facts must be borne in mind; the condition of the blood in normal dogs is

not comparable to that in patients with polycythemia vera, and the reaction of these animals to phenylhydrazine may be different as a result of the difference in species. We have, however, attempted to duplicate as nearly as possible the clinical administration of phenylhydrazine.

# Experiments With Phenylhydrazine†

## II. Studies On Renal and Hepatic Function and Erythropoiesis\*

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and

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LEVI (8) first remarked on the danger of inducing permanent changes in the liver by treating cases of polycythemia vera with phenylhydrazine. He reported a case in which 7.5 gm. of phenylhydrazine hydrate had been administered in eighteen months. Death occurred from erysipelas. Necropsy showed cirrhosis of the liver, but Levi did not consider the drug necessarily causal, as cirrhosis of the liver is often noted in cases of polycythemia vera untreated with phenylhydrazine. Studies of the function of the liver following the administration of phenylhydrazine have not been numerous. Brown and Giffin (1296) (3) were unable to demonstrate dye retention in patients after single courses of treatment with a total dosage of from 3 to 6 gm. of the drug. Several of their cases which have been studied since that report, after three or four courses of treatment, do not show dye retention. Stealy's (9) patient has been treated for three years without manifesting gross evidence of hepatic injury, and functional studies showed no change. Leopold (6) noted absence of dye retention in one case after the administration of 2.0 gm. of the drug.

Bodansky (10) gave 360 mg. divided into four doses to a dog weighing 5.9 kg. Studies on the carbohydrate tolerance gave evidence of marked hepatic injury. This dosage would be equivalent to 1 gm. of phenylhydrazine each day for four days for a man weighing 70 kg., a much larger dose than that which is used therapeutically. Moreover, there is no evidence that the injury was more than temporary. Long (7) gave rabbits weighing 2 kg. 3 mg. intraperitoneally in a single dose and found a slight lag in the excretion of tetrachlorphenolphthalein.

Studies of renal function in experiments with phenylhydrazine are much more infrequent than those on the liver. Brown and Giffin reported no change after single courses. Since then some of their cases in which repeated courses were given have shown no evidence of reduction in renal function. In Stealy's case treated

\*The material in this paper was presented in a thesis by Edgar V. Allen to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Medicine, 1928.



with phenylhydrazine for three years blood urea and excretion of phenolsulphonephthalein were normal.

#### EXPERIMENT I. THE EFFECT OF PHENYLHYDRAZINE ON RENAL AND HEPATIC FUNCTION

Three dogs were each given 146 daily doses of phenylhydrazine in a period of eight months (fig. 13 Study I). The function of the kidneys was studied by means of the phenolsulphonephthalein test, blood urea and urinalysis. The hepatic function was studied by the dye excretion method and the data are shown in the tabulation. The final readings in each instance were taken one month after phenylhydrazine had been discontinued. A survey of the tests shows that during the nine month period there was an average diminution of 27 per cent in the phenolsulphonephthalein excretion by the kidneys. Urinalyses showed no change. Whether this diminution in phenolsulphonephthalein excretion is significant cannot be predicated. The final readings of the phenolsulphonephthalein excretion in each instance were within normal limits. The absence of abnormal urinary conditions would indicate absence of acute processes in the kidney and the absence of marked organic lesion. In some instances, while phenylhydrazine was being administered, the blood urea was slightly increased, but not permanently. This has also been shown clinically by Huffman, (1) and Brown and Giffin. The former believed this was largely due to "renal flooding." These data indicate that the excretive function of the kidneys for

nitrogenous products is adequate, but it is possible that the margin of safety has been encroached on. Studies of hepatic function by the dye excretion method showed only slight retention of dye in one of three animals (Dog *b*, tabulation). Dogs *b* and *c* (tabulation) were killed and necropsy was performed. The pathologic aspects will be discussed in Study III.

#### EXPERIMENT 2. THE EFFECT ON ERYTHROPOIESIS

The rate of regeneration of erythrocytes was studied after various lengths of time in order to determine the effect of the drug on the erythropoietic function of the body. The results are shown in figure 13 Study I and figures 1 and 2. Fig. 13 shows the rate of increase in the number of erythrocytes beginning at the end of the third week following six daily doses, at the end of the fourteenth week following seventy daily doses, and at the end of the thirty-second week following 146 daily doses. Figures 14 and 15 show the results in dogs *a* and *c* illustrated on a larger scale. The three curves show but little variation and indicate that regeneration occurs as rapidly after prolonged phenylhydrazine administration as it does after a very short course. The number of erythrocytes did not remain at a new and lower level after prolonged phenylhydrazine administration, and there was no indication that the erythropoietic function of the body was depressed.

In all three animals a peculiar cycle of anemia occurred after the complete withdrawal of the drug (fig. 13, June

TABLE I

THE EFFECT OF PROLONGED ADMINISTRATION OF PHENYLHYDRAZINE ON FUNCTION OF THE LIVER AND THE KIDNEYS

Dog	Date, 1927	Renal function		Hepatic function,	Specific gravity	Urine					Carbon dioxide combin- ing power, volume, per cent	Blood chlorides, mg. per cent
		Phenol- sulphone-- phthalein, per cent	Blood urea, mg. p.c.			Graded 0 to 4						
						Albumin	Casts	Erythro- cytes	Leuko- cytes	Sugar		
a	1-27		60								48	610
	2-23	75	30								44	689
	4-13		27	0								
	4-20	75	36		1.032	I	0	I-	I	I-		
	7-5	50	42	0	1.033	I	0	I-	2	0		
	7-28	40	34	0	1.031	I	0	0	I	0		
b	1-27		20									660
	2-23	75	23								58	680
	4-6		27									
	4-20		27									
	7-5	20-45	23	0	1.030	3	0	I-	I	I		
	7-28	60	16	I	1.007	I	0	0	0	0		
c	2-21		25								52	700
	2-23	90	15								39	690
	4-13		17	0								
	4-20	90	16		1.010	I	0	0	0	0		
	7-5	50	18	0	1.011	I		I-	I-			
	7-28	60	10	0	1.012	I	0	0	0	0		

22). The return to normal was similar to that which, from clinical and previous experimental study, one would expect. After a period, during which the number of erythrocytes was normal, anemia occurred in much the same manner as if phenylhydrazine had been given. After a prolonged period of anemia the count rose again to normal

more slowly than is usual following phenylhydrazine administration.

### EXPERIMENT 3. THE EFFECT OF SPLENECTOMY

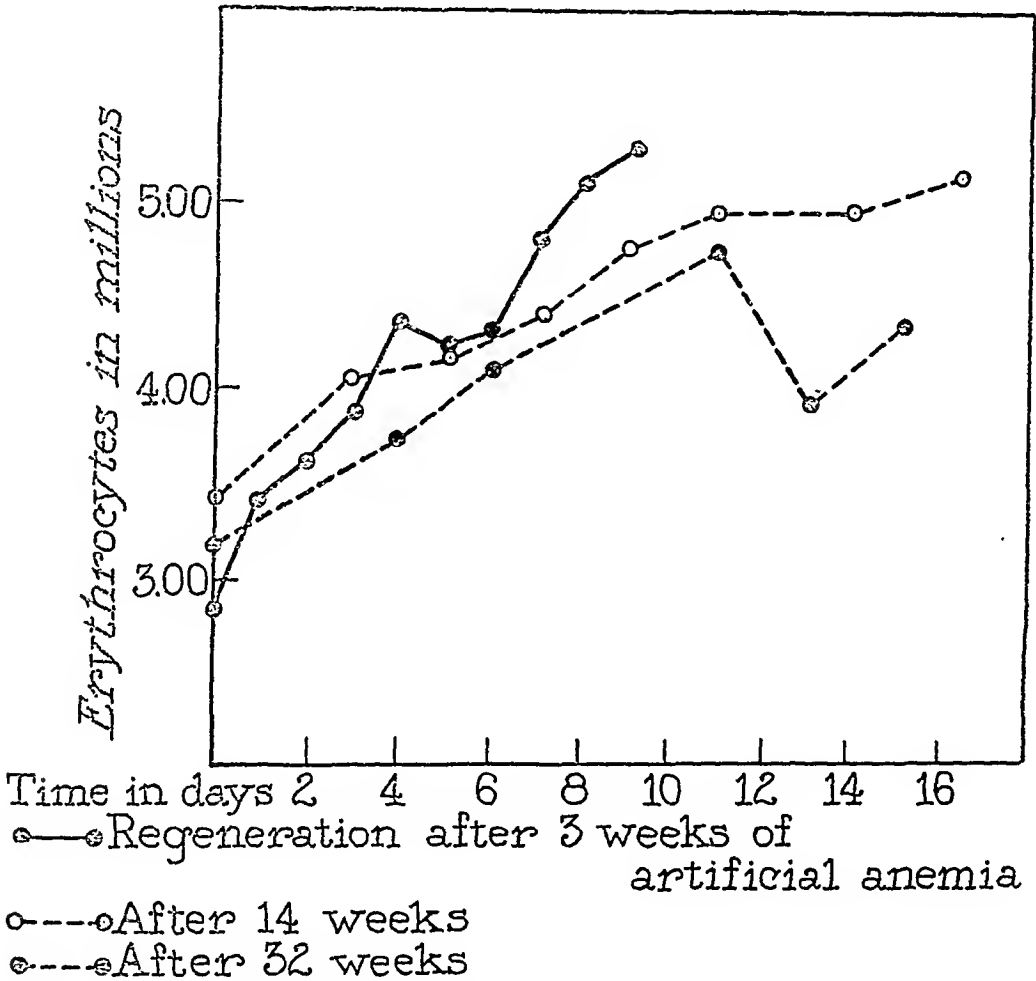
Splenectomy had no effect on the action of phenylhydrazine on the erythrocytes in two dogs. This fact eliminates the spleen as the site of action.

Long has previously reported a similar result in rabbits.

SUMMARY

Each of three dogs was given a total dosage of approximately 1.26 gm. of

There was an average reduction of 27 per cent in phenolsulphonephthalein excretion, but the final readings were within normal limits. Urinalyses were negative; blood urea estimations were normal. These data indicate that the



FIGS. 1 and 2. Rate of regeneration of erythrocytes after treatment with phenylhydrazine.

phenylhydrazine hydrochloride over a period of eight months, the equivalent of from four to six years of clinical treatment in man. The final studies of renal and hepatic function were made one month after the drug had been discontinued.

renal function was adequate after prolonged treatment, but they do not prove that the kidneys were not impaired by the drug.

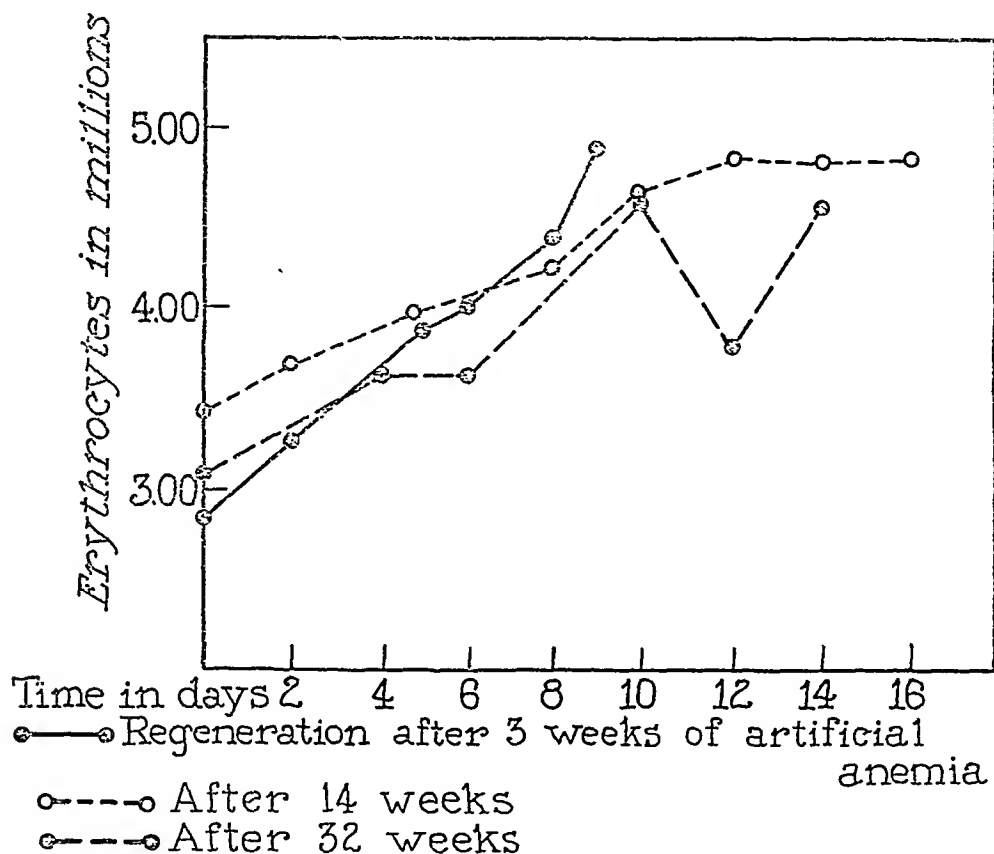
Only one of three dogs receiving similar amounts of phenylhydrazine showed reduction in dye excretion

from the liver. This change was small and of questionable significance. The rate of regeneration of erythrocytes was unchanged.

The removal of the spleen was without influence on the effect of phenylhydrazine on the number of erythrocytes.

The treatment of erythremia with phenylhydrazine. *Jour. Am. Med. Assn.*, 1925, lxxxv, 2027-2032.

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# Experiments With Phenylhydrazine

## III. Pathologic Anatomy\*

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IN Studies I and II methods were suggested which were believed essential for a comprehensive survey of the effects of phenylhydrazine. In brief these are: the effect on the blood, the effect on the function of the liver and kidneys, the effect on erythropoiesis, and the pathologic changes induced by prolonged administration of phenylhydrazine in doses sufficient to affect the erythrocytes which is comparable to that produced clinically. Criticism of conclusions drawn from previous work was that they were not based on results following experimental dosage comparable to that used clinically, and that results following the use of compounds allied to phenylhydrazine were too often regarded as produced by phenylhydrazine itself. The preceding studies included experiments on the blood, on the function of the liver and kidneys and on erythropoiesis. This report is on the results of a study on the pathologic anatomy.

Records in the literature with regard to the effect of phenylhydrazine on the structure of organs have not been numerous. Underhill (1) gave 50 mg. of phenylhydrazine to a dog weighing

10 kg. Since he was interested primarily in the effect on the blood sugar, he did not report the effect on the erythrocytes nor the time of necropsy. At necropsy all organs appeared normal except the liver and spleen, the former of which was of a peculiar chocolate-brown color. The spleen was enormously enlarged and dark. Microscopic studies were not reported. It seems probable to us that the changes in the liver and spleen were temporary and due to destruction of erythrocytes. Levi (2) reported the necropsy data in a case of polycythemia vera treated with phenylhydrazine. The patient was a man aged fifty years who had received 7.5 gm. of phenylhydrazine in a year and a half and died following erysipelas. At necropsy the spleen was enlarged, was rich in leukocytes and contained excessive blood pig-

\*Submitted for publication February 9, 1928.

The material in this paper was presented in a thesis by Edgar V. Allen to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine, 1928.

ment. The liver was of medium size with a slightly irregular surface and on section was of a peculiar yellowish color. Histologic study showed marked increase in the interlobular connective tissue which contained many round cells. Centers of regeneration were present. He believed that phenylhydrazine did not cause the cirrhosis but that this was due primarily to increased destruction of blood since it occurred in untreated cases; the phenylhydrazine may have exaggerated the normal course of events by increasing the destruction of blood. According to Owen (3), "whether repeated small doses of phenylhydrazine such as were given to patients will or will not be deleterious to the liver cannot be said yet." Bodansky (4) gave a dog weighing 5.9 kg. subcutaneous injections on four subsequent days, a total dose of 360 mg. of phenylhydrazine hydrochloride. Rapid reduction in the number of erythrocytes occurred and the animal was killed on the twentieth day. The spleen was greatly enlarged and microscopically showed hyperplasia and hematogenous pigmentation. Fatty changes were present in the cortical portion of the kidneys. The liver showed extensive "degenerative and necrotic changes" and hematogenous pigmentation. It seems essential to point out that the dosage in this experiment is the equivalent of 1 gm. of phenylhydrazine given daily for four days to a man weighing 70 kg. which is much more than a therapeutic dose. Long (5) gave rabbits weighing 2 kg. each a single dose of 30 mg. intraperitoneally. He found no histologic change in the liver. The spleen, lymph nodes and bone marrow

contained a markedly increased number of phagocytic cells containing intact erythrocytes and increased pigmentation.

#### EXPERIMENT I

The dog used in this experiment was given 146 daily doses of phenylhydrazine hydrochloride by stomach tube in a period of eight months.\* The amount was regulated to produce a moderate grade of anemia\*\* and to simulate that used clinically in the treatment of polycythemia vera. The total dosage was 1.26 gm. for each kilogram of body weight, an amount sufficient in a case of polycythemia vera for from four to six years. Death was induced by the injection of air into the femoral vein twelve months after the beginning of the experiment and four months after phenylhydrazine had been discontinued. Complete necropsy was performed.

*Gross examination.*—The peritoneal and pleural cavities appeared normal. There was a slight amount of blood and air in the pericardial cavity. The epicardium, myocardium and heart valves did not show pathologic changes. The lungs appeared normal throughout. The spleen was of normal size. The cut surface was dark purplish brown with irregular still darker areas scattered throughout the substance. The liver was dark reddish brown. There were about ten scattered, discrete, grayish nodules just beneath the capsule measuring from 1 to 3 mm. in diameter. The cut surface appeared

\*The functions of the liver and kidneys are reported in Study II, tabulation.

\*\*Study I, figure 13.

normal and no other nodules were found. The gastro-intestinal tract, pancreas and adrenals did not show change. The kidneys were about equal in size. The capsules stripped easily leaving dark brown surfaces on which there were numerous irregular pits and scars, linear and roughly circular in

creas, lymph nodes, and thyroid and axillary arteries stained with hematoxylin and eosin and the van Gieson stain did not show changes.

The kidneys appeared normal except for the scars already described. In the cortical portions of these the glomeruli were well preserved except that the

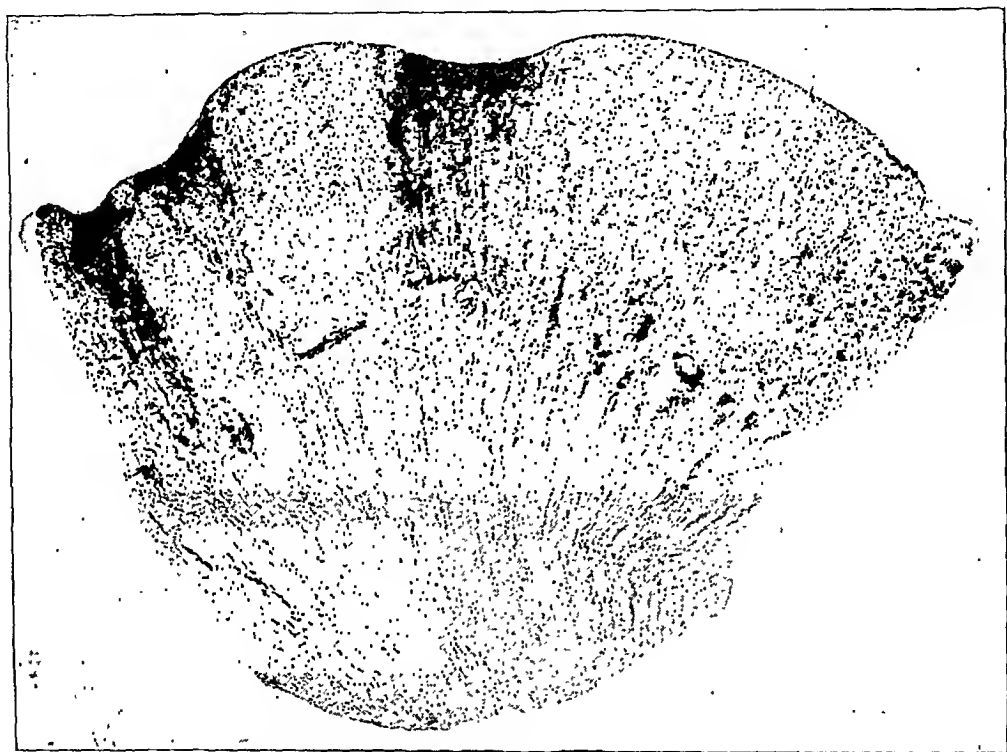


FIG. 1. Depressions and connective tissue scars in the cortex and medulla of the kidney. The glomeruli are well preserved.

shape. The cut surface showed that these scars were paler than the remainder of the renal parenchyma and were roughly pyramid shaped, their apexes extending well down through the cortex into the medulla, but not apparently to the pelvis (fig. 1). The kidneys otherwise appeared normal. The bladder and genitalia appeared normal.

*Microscopic examination.*—Sections of the myocardium, lungs, spleen, pan-

tufts were slightly contracted and ischemic. In some, Bowman's capsule was slightly thickened. Very few tubules remained and these only as fragments. They were replaced by connective tissue consisting of a few lymphocytes and a larger number of endothelial and plasma cells with interspersed longitudinal bands and a scattered network of fibrous tissue. There were large areas of compact fibrous



tissue around some of the larger arteries near the corticomedullary junction. In the medulla the scarred area consisted of a rather dense fibrous-tissue stroma in which were constricted collecting tubules. These scars were definitely delimited from the normal renal parenchyma (fig. 2). Sections specially stained showed no more fat than the kidney of a control dog. By special staining there was no iron (hemosiderin) except in the pyra-

the capsule down to and around a portal space (fig. 3). A few other portal spaces were crowded with lymphocytes and in a few places these were found in the walls of the blood vessels. There were a few small collections of lymphocytes in capillary spaces, and a few around central veins. By special staining the amount of iron in the liver was found to be increased (grade 1), most of it phagocytosed and closely packed in large

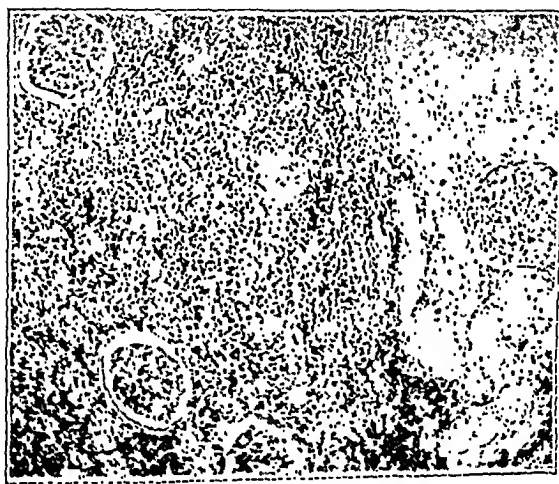


FIG. 2. Cortical portion of a cellular connective tissue scar in a kidney. The scar is definitely delimited and the glomeruli are well preserved.

midal scars which contained a rather large amount, most of it closely packed in large phagocytic cells.

The liver showed rather large pale parenchymal cells, close together, with a small amount of vacuolization which was present also in the liver of the control dog. There was rather marked capillary congestion. No fat was seen in the sections stained with scarlet red. A small grayish-white subcapsular nodule, one of those seen grossly, was found to be a collection of lymphocytes which extended from

histiocytes and small amounts scattered diffusely in blood capillaries and in the connective tissue around the portal spaces. By special staining the amount of iron in the spleen also was shown to be increased (grade 1).

#### EXPERIMENT 2

This experiment was carried out in a manner comparable to the first experiment\*. The animal was killed thir-

\*Studies I and II, figure 13 and Tabulation.

teen months after the beginning of the experiment and five months after phenylhydrazine had been discontinued. Complete necropsy was performed.

*Gross Examination.* — The peritoneal cavity contained a few loose, easily broken, fibrous adhesions over the loops of small intestine, the omentum and the transverse colon. The

tended just below the capsule. The substance of the liver was dark brown and homogeneous with indistinct markings. The stomach, intestines, pancreas and adrenals appeared normal. The left kidney had been removed one month previously. The pedicle remained as a clean healed amputation stump. The right kidney was normal in size. Its capsule stripped easily

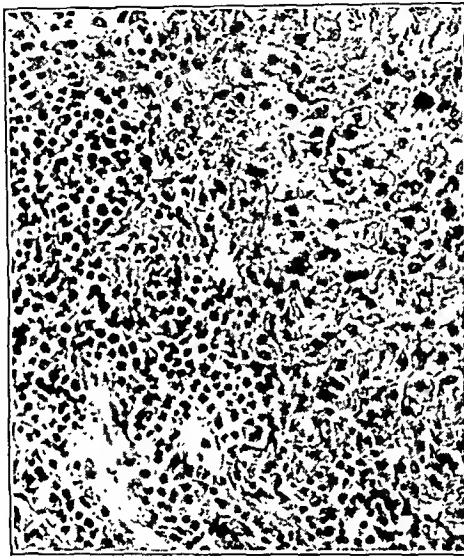


FIG. 3. A collection of lymphocytes beneath the capsule of the liver extending down to a portal space. The hepatic cells are normal.

pleural and pericardial cavities, and the lungs and heart appeared normal. The spleen was small and firm with numerous thickened, irregular, single and confluent, grayish-white areas in the capsule (hyaline perisplenitis). On the cut surface the trabeculae and malpighian corpuscles were distinct and close together. The liver was firm and deep purplish-brown with several darker brown areas measuring from 6 to 10 mm. in diameter on the surface. On the cut surface these ex-

leaving a smooth brown surface on which there were a few scattered small pits. The cut surface appeared normal. The bladder was thick-walled, but its mucosa appeared normal. The genital organs appeared normal.

*Microscopic examination.*—Sections of the lungs, pancreas, adrenals, iliac arteries, aorta, pectoralis major muscle and aortic lymph nodes, stained with hematoxylin and eosin and the van Gieson stain did not show anything

abnormal. The capsule of the spleen was irregularly thickened and composed of dense fibrohyalinized tissue with a few cell nuclei. The iron was increased (grade 1). The trabeculae were more numerous and closer together than normal. The liver showed rather large pale cells, crowded close together. No fat could be demonstrated. The darker areas observed by gross examination proved to be irregular subcapsular hemorrhages extending a short distance into the substance of the liver. There were no collections of lymphocytes. There was increased iron (grade 2) closely packed in large cells and deposited irregularly in some of the blood capillaries and in the connective tissue around the portal spaces.

### EXPERIMENT 3

The dog used in this experiment was given 80 mg. of phenylhydrazine hydrochloride for each kilogram of body weight daily by stomach tube. The dog was moribund on the fifth day when he was killed by injecting air into the jugular vein. Complete necropsy was performed immediately.

*Gross examination.*—The blood was brown and did not coagulate easily. The pleural and pericardial cavities appeared normal. There were numerous brown nodules from the size of a pin-point to 3 mm. in diameter, in the omentum and in the fat around the pedicle of the spleen (apparently hemorrhages); otherwise the peritoneal cavity was normal. The myocardium was brown and the lungs were a peculiar brownish-gray. The spleen was firm and approximately normal in

size. Its capsule was slate-gray and normally wrinkled. The cut surface was black and the corpuscles and trabeculae could not be seen. The liver was dark greenish-brown with a few small black areas on the surface from 2 to 3 mm. in diameter. The cut surface was greenish-brown and the normal markings were not seen. The gallbladder was distended. The stomach, intestines, pancreas and adrenals were slightly browner than normal, otherwise there was no change. The kidneys were chocolate-brown and there were a few irregular darker areas on the surface. They appeared swollen and tense. The capsules stripped easily when cut and the edges everted. The cortical striae were distinct, particularly at the corticomedullary juncture where they were alternately dark brown and light tan. Several dark brown patches extended through the cortex and outer portion of the medulla. There were a few submucous hemorrhagic areas in the urinary bladder. The genital organs appeared normal.

The myocardium, lungs, pancreas, adrenals and pectoralis major muscle when stained with hematoxylin and eosin and by the van Gieson method did not show changes except that the capillaries were engorged with blood cells and blood pigment. The malpighian corpuscles of the spleen were few and small. There was a marked decrease in the number of leukocytes. The sinusoids were dilated and packed with yellowish-brown material which apparently was blood pigment and erythrocytes in many stages of disintegration. However, there was no

more iron than seen in the spleen of the control dog. This was scattered diffusely and was pale-staining. The hepatic cells were smaller than normal and rather granular and deeply stained. The capillary spaces between them were dilated and contained in many places a rather large amount of blood pigment and disintegrated erythrocytes, some in small compact groups and some scattered diffusely

with small iron granules and there was iron in the debris in their lumina (fig. 5). Iron was seen occasionally in the glomerular spaces also, but there was none in the glomerular cells or in the distal convoluted, Henle's loops, or collecting tubular cells. In the spleen there was approximately a normal amount of iron but it was scattered diffusely and pale-staining. In the cells of Henle's loops there was

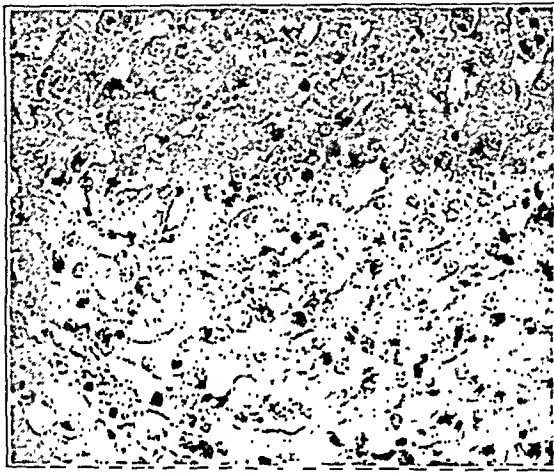


FIG. 4. Slight atrophy of the parenchymal cells of the liver and the dilated capillary spaces containing blood pigment and numerous phagocytic cells.

(fig. 4). No fat was seen. There was an abnormally large amount of rather pale-staining iron scattered diffusely throughout the capillary spaces, some of it apparently phagocytosed in large cells. The renal glomeruli appeared normal. The cells of the convoluted tubules were somewhat fragmented and irregularly stained, and appeared coarsely granular. There were several large irregular cystic spaces in the cortex, some of them containing small amounts of blood pigment. The cells of the proximal convoluted tubules throughout the cortex were packed

considerably more than the normal amount of fat.

#### EXPERIMENT 4

This experiment was performed like the third experiment. The animal died on the fifth day. The body was placed at a temperature below freezing. Specimens from the liver and kidney were removed approximately sixteen hours after death. Complete necropsy was not performed.

*Microscopic examination.*—The hepatic cells, stained with hematoxylin

and eosin, appeared even more shrunk-  
en and deeply staining than those in  
the third experiment. The atrophy  
was particularly prominent around the

phagocytes (fig. 6). However, iron  
could not be demonstrated. Sections  
stained with scarlet red did not show  
fat. The cells of the renal tubules



FIG. 5. Iron in a kidney, especially stained. The iron is the dark stained material in the lumina and cells of the convoluted tubules.

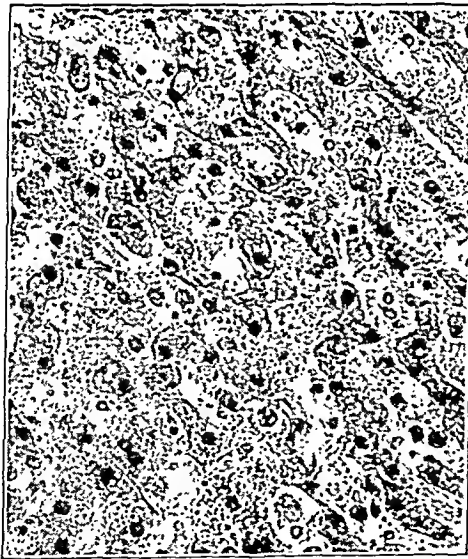


FIG. 6. Marked atrophy of the parenchymal cells of the liver, dilatation of the capillary spaces by blood pigment and numerous phagocytic cells.

central veins and portal spaces with  
corresponding dilatation of the capil-  
lary spaces. The latter contained  
scattered blood pigment and many

were swollen and granular but fairly  
homogeneous (perhaps a postmortem  
change). In one section there were  
two rather large areas and numerous

smaller areas well beneath the surface which contained large numbers of plasma cells and endothelial cells closely packed together, crowded into and widely separating the interstices between the tubules and around the glomeruli. Near the centers of these collections of cells the tubules were

proximately sixteen hours after death. Complete necropsy was not performed.

*Microscopic examination.*—The cells of the liver were shrunken and deep-staining. The capillary spaces contained blood-pigment-filled phagocytes

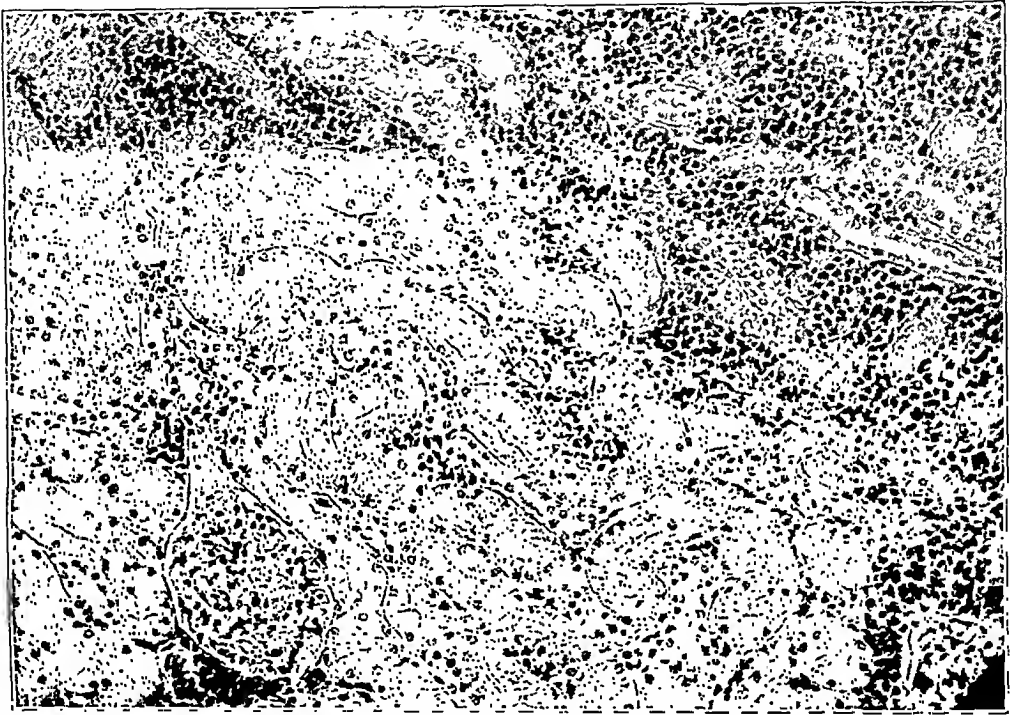


FIG. 7. Interstitial collections of plasma and endothelial cells in a kidney. The structure is otherwise normal.

constricted and atrophic (fig 7). There was no increase in fat. The same amount of iron was present in the proximal convoluted tubular cells and in the lumina of the tubules as in the third experiment except that it was more finely divided.

#### EXPERIMENT 5

This experiment was similar to the fourth experiment. Specimens of the liver and kidneys were secured ap-

and scattered erythrocytic debris. The changes were similar to those observed in the third experiment and less marked than those observed in the fourth. Iron and fat were absent as in the fourth experiment. The kidney resembled that in the fourth experiment except that there were no interstitial collections of cells. There was more iron, but no fat was seen in sections stained with scarlet red.

*Comment on Experiments 1 and 2.*

—Our studies showed that the lesions found were restricted to the spleen, liver and kidneys. The spleen observed in the second experiment was small and fibrotic and showed definite changes of hyaline perisplenitis which were not present in the spleen observed in the first experiment. This was probably incidental with no bearing on these experiments. The liver observed in the first experiment showed scattered small collections of lymphocytes. These were not present in the liver studied in the second experiment and their significance is indeterminate but probably also incidental. There were small subcapsular hemorrhagic areas in the liver in the second experiment. These were so recent that phenylhydrazine as an etiologic factor can readily be dismissed. In general, observation of livers in both experiments showed them to be remarkably normal. There were large scars in the kidneys in the first experiment and smaller ones in the kidneys in the second experiment. These contained some fibrous tissue which appeared to be of recent formation. The tubules in the scars were profoundly affected, but the glomeruli were practically spared. The scars are not true infarcts but their situation and shape are strongly suggestive of a vascular rather than an ascending infectious origin. They resemble closely some of the scars found in the kidneys of elderly human beings with arteriosclerosis which are presumably due to slow progressive ischemia. Although iron occurs normally in small amounts in the

spleen and liver of normal dogs, it was definitely increased in these experiments, doubtless the remains of larger amounts deposited during periods of active destruction of blood. Detailed study was made of the blood vessels, particularly the arterioles, in all the histologic material examined and we finally concluded that there were no significant changes in the media or intima and no increase in the periarterial connective tissue. We are of the opinion that none of the abnormal findings in these two experiments was due to the phenylhydrazine itself, except the evidence of the destruction of erythrocytes and hemoglobin.

*Comment on Experiments 3, 4, and 5.*

—The pathologic anatomy observed in the third experiment may be summarized as follows: (1) evidence of hemolysis and hemoglobin destruction; (2) hemorrhagic areas in the omentum possibly due to hemolysis or to toxemia; (3) marked reduction in leukocytes of the spleen; (4) atrophy of the parenchymal cells of the liver, and (5) overloading the convoluted tubules of the kidney with iron. Much of the iron in the liver and spleen of this dog was in a rather diffuse form, apparently it was being produced much faster than it could be phagocytosed. In the kidney the tubular epithelium and possibly the glomeruli also were apparently excreting the iron but it was piled up in the tubules, probably much more rapidly than it could be taken care of. Observations in the fourth and fifth experiments confirm this phenomenon in the kidneys and show changes in

the liver similar to those observed in the third experiment except that iron was absent. An observation which is difficult to evaluate is the rather extensive interstitial inflammatory reaction in the kidney in the fourth experiment particularly since nothing similar was found in the kidneys in the third and fifth experiments. This change might occur directly as a result of phenylhydrazine but its localized inflammatory nature and the absence of such a lesion in the third and fifth experiments suggest that it is an incidental observation. The atrophy of the liver is probably a direct result of the large doses of phenylhydrazine either by direct toxic action or by pressure from capillary spaces hugely engorged with disintegrating erythrocytes and large phagocytic cells.

#### SUMMARY

Two dogs were given 146 daily doses of phenylhydrazine hydrochloride in a period of eight months in amounts sufficient to produce an effect on the erythrocytes comparable to

that desired in the clinical use of phenylhydrazine. The total dosage, calculated on body weight, was equivalent to that necessary in the treatment of the usual case of polycythemia vera for from four to six years. Necropsy and histologic examination four and five months, respectively, after phenylhydrazine had been withdrawn and twelve and thirteen months after the beginning of the experiments showed nothing abnormal which could be definitely attributed to phenylhydrazine, except increased deposition of iron in the liver and spleen.

One dog was given doses of phenylhydrazine which were lethal in six days. The only significant evidence which could be definitely attributed to phenylhydrazine, per se, was that of rapid destruction of erythrocytes and hemoglobin, atrophy of the parenchymal cells of the liver, reduction in the number of the splenic leukocytes, and overloading of the cells of the renal convoluted tubules with iron. Partial necropsy on two dogs given similar doses showed the same changes in the liver and kidneys.

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# Tetany and Chronic Diarrhea\*

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THE infrequency of tetany as an accompaniment of diarrhea is attested by the fact that most contemporary writers on tetany rarely discuss diarrhea as an etiologic factor. The subject is barely mentioned by MacCallum, and Dock and Lissner. Barker describes "tetania colonica" which he says may be produced in predisposed persons by dilatation and obstruction at any point in the intestinal tract. Critchley, in reviewing the pathogenesis of tetany, speaks of the intestinal and colonic types of the syndrome, and enumerates certain recorded causes. Trousseau, in his celebrated lecture on tetany, in which the sign bearing his name is described, states that, "of the pathologic conditions (causing tetany) diarrhea, especially when abundant and chronic, is the one which exerts the most striking influence." He cites the frequent occurrence of tetany during the cholera epidemic of 1854 in support of this contention. However, if one is to judge by the literature, diarrhea is one of the least common causes of tetany in the adult. A few reported cases and certain recent experimental studies cast some light on the subject. We propose here to report a case of tetany of this type, to review the literature concerning it, and record the results of treatment by parathormone.

A married woman, aged thirty-one, who had resided in northern Wisconsin all her life, came to the Mayo Clinic in June 1927. She was one of a family of ten children; her parents and all her brothers and sisters were alive and well. Her general health had been fair except for an attack of influenza in 1920, and tonsillectomy performed during the same year. However, she had always been small and rather frail, and had suffered occasionally from diarrhea since early childhood. In 1920, she had noticed that in using a pencil her fingers became cramped and stiff and that in walking rapidly her legs cramped, but she regarded these symptoms as of little importance. She was married in 1921, and one year later, during the fourth month of pregnancy, tingling and numbness of the hands with marked stiffness of the muscles of the right arm developed. She recalled having had a definite carpal spasm at this time lasting about six hours. During the next two weeks she had three similar attacks. The pregnancy terminated in stillbirth at eight months. She recovered her usual health slowly during the following year. In 1923, at long intervals, definite but mild spasms occurred in the muscles of the hands. She had always suffered more or less from flatulence and abdominal distress, particularly after the ingestion of fat food. At intervals since 1922 she had had rather severe attacks of diarrhea lasting about two weeks; in describing these attacks, she mentioned that diarrhea brought on the attacks of tetany. In 1926 she had suffered from vomiting and diarrhea for

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nearly two months; she lost 20 pounds in weight and while she noticed some stiffness and numbness of the hands there was no definite tetany. In April 1927 an attack of diarrhea was followed by paresthesia, numbness, and stiffness of the hands and she was totally incapacitated. Shortly afterward definite carpal spasms developed which finally brought her to the clinic. In giving the history the patient was inclined to lay great stress on the gastro-intestinal disturbances, and was convinced that they were responsible for the peculiar numbness and cramping of her hands.

The patient was 5 feet in height and weighed 76 pounds. The systolic blood pressure was 82, and the diastolic 60. Temperature, pulse, and respiration were normal. There was slight darkening of the skin over the exposed areas of the body; the mucous membranes were not pigmented and there was no accentuation of the pigment over the malar surfaces and the forehead. The most striking symptom was the carpal spasm which appeared spontaneously at various times during examination. Examination of the heart, lungs and abdominal and pelvic organs was essentially negative, as was the ophthalmologic examination except for slight horizontal nystagmus. Slight marginal glossitis was noted but there were no other oral lesions. Neurologic examination was objectively negative except for strongly positive Chvostek's and Trousseau's signs. Difficulty was encountered on attempting to study the electric reactions, the patient's hand going into tetany as soon as the electrode was placed on the ulnar nerve. Urinalysis was negative. The blood Wassermann reaction was negative. The hemoglobin was 75 per cent, the erythrocytes numbered 4,000,000 and the leukocytes 7,000. The differential count was negative except for a slight relative increase in lymphocytes (27 per cent). A test meal showed free hydrochloric acid 34, and total acidity 50. The stools contained fat but no parasites or ova. Roentgenograms of the spine were negative; stereoscopic plates of the chest showed a healed tuberculous lesion of the right upper lobe.

The volume index of the blood was 0.87. Two blood calcium readings showed 6.3 mg. and 6.7 mg. for each 100 c.c.

Being somewhat at a loss to explain the cause of the tetany, we urged the patient to go to the hospital for further study. She was unable to stay, however, and was dismissed with instructions to follow a high vitamine diet and to take cod-liver oil. She was also given desiccated thyroid, 1 grain daily, and calcium lactate in teaspoonful doses three times a day.

At the end of a month she wrote that she had gained 10 pounds in weight, had been free from tetany and paresthesia, and in general had been doing well except for flatulence and mild epigastric distress after meals. In September a letter stated that she had suffered from severe diarrhea all of the month of August and had lost about 5 pounds in weight. There had also been mild carpal spasms and rather annoying paresthesia of the hands. Menstrual periods had been irregular and scanty and the patient raised the question of possible pregnancy. She wrote again in October to tell us that all previous symptoms had recurred and with more severity. A generalized convulsion had occurred with marked spasms of the hands and feet but without loss of consciousness. A week later there were three attacks in one day. She described these as very painful, and associated with great difficulty in speech and in swallowing. She had lost 12 pounds in weight and she had not menstruated since August. She returned to the clinic October 24, and was admitted to hospital for observation and treatment.

The patient was found to be in much the same condition as on the previous visit. The blood pressure was still low, 86 systolic and 56 diastolic. Ferenczi-Poole's, Chvostek's, and Trousseau's signs were present. The hands went into the obstetric position after slight increase in respiration which is necessary for an examination of the chest. A gynecologist reported the pelvic organs to be normal; no evidence of pregnancy was found. The patient again emphasized the relation of diarrhea to the attacks of tetany

and said that she was sure she could get along without trouble if her digestion and bowels were in better condition.

The laboratory examinations were all repeated with negative results except that the blood calcium was low, 7.1 mg. for each 100 c.c. There was moderate secondary anemia; the hemoglobin was 54 per cent, erythrocytes numbered 3,600,000 and the leukocytes 7,500. The blood urica was 18 mg. for each 100 c.c., and the carbon dioxide combining power of the blood plasma 48 volumes per cent. Roentgenograms of the stomach, sella turcica, spine, gallbladder, and colon were negative. The diarrhea which had begun during the previous month had subsided somewhat, but there were still one or two large offensive fatty gray stools daily; the stools were not foamy at any time. The high content of fat in the stools was confirmed by chemical and microscopic examinations. A careful search for parasites and ova was made with negative results. Two groups of stool cultures with taurocholic acid medium were negative for *Monilia psilosis*. The basal metabolic rate on two occasions was  $+12$  and  $+10$  per cent. After a period of observation it was felt that the patient's contentions in regard to the relation of diarrhea to the tetany were probably correct. She was able to recall an attack of diarrhea preceding all of the major and most of the minor attacks of tetany, the one exception being the attack which had occurred during pregnancy. It was suggested that either pancreatic infantilism or sprue might be the etiologic factor. The latter could not be definitely confirmed in the absence of *Monilia* in the stools, although there was much to suggest it. The theory of infantilism seemed to rest on somewhat better grounds, in view of the history of diarrhea and undernutrition since early life. Because of the possibility of pancreatic disease, a test for glucose tolerance was made with results as follows: fasting blood sugar 90 mg. per cent; the blood sugar a half hour after 100 gm. of glucose was given was 99 mg. per cent, after one hour 68 mg. per cent, and after two hours 82 mg. per cent. This

seemed a rather abnormally high tolerance, although diminished absorption from the intestine could not be excluded.

The patient was placed on treatment consisting of high-calcium, high-vitamine diet, 1 dram of calcium lactate, three times a day, and 15 units parathormone on alternate days. Under this regimen the blood calcium rose rapidly to normal and the symptoms and signs of tetany disappeared; the patient gained in weight and felt well, although she still suffered from flatulence and epigastric distress after meals. The electric reactions were checked three days after the first dose of parathormone, at a time when the blood calcium was 9 mg. for each 100 c.c. The cathodal closing contraction occurred at 0.5 milliamperes and the cathodal opening contraction at 3.5 milliamperes. These figures represented improvement so far as the tetany was concerned. The anemia also improved, the hemoglobin rising to 63 per cent (Dare) and the erythrocytes to 4,120,000. Since the gastro-intestinal symptoms were still troublesome and because of the probability of deficient fat absorption a change to a high-protein, high-vitamine diet was made shortly before the patient's dismissal; this resulted in practically complete relief of abdominal symptoms. As might have been expected, however, the serum calcium fell somewhat. At the time of her dismissal she was instructed to continue the high-protein diet with 10 units of parathormone on alternate days, and calcium lactate in the dosage given previously.

A letter received three weeks after the patient reached her home was very encouraging. She had gained 7 pounds and there were no signs of tetany. She had suffered slightly from flatulence. A blood calcium determination at the Children's Hospital in Milwaukee was reported as 11.3 mg. for each 100 c.c. The last report was received two and a half months after dismissal. Her weight was 93 pounds, a gain of 15 pounds, and she was well satisfied with her progress; she said she felt very much better and stronger than she had for some time. She had menstruated normally in December and

in January. December 26, 1927, the blood calcium was 11 mg.

During the month of January the patient had suffered from a mild recurrence of diarrhea and had noticed paresthesia of the extremities. January 26 the blood calcium was 7.84 mg. She was still somewhat troubled by flatulence although less than before. The use of pancreatin had eliminated most of the indigestion and postprandial distress. She was advised to increase the dose of parathormone from 10 units to 15 units on alternate days and to eliminate all fat from the diet until the diarrhea subsided. It was also suggested that the dose of parathormone be reduced later, when the blood calcium had returned to a normal level.

#### COMMENT

The features of this case meriting special discussion are (1) the chronic recurring diarrhea followed by tetany, (2) the striking constitutional and nutritional defects, and (3) the prompt response to treatment with parathormone. As has been stated, the production of tetany by chronic diarrhea is not a common occurrence in the adult. Sonrier (1877) reported the case of a woman who suffered for six years from recurrent diarrhea; for two years these attacks had been followed by severe tetany. He was unable to explain the condition satisfactorily, but mentioned the "celiac flux" described by Trousseau as a possible factor.

Griffith, reviewing the subject of "Tetany in America" (1895) noted only two cases of this type. The first, (Mills, 1879) was that of a girl aged sixteen, who, following rheumatic fever, suffered from diarrhea which was in turn complicated by moderately severe tetany. The whole process was of short duration, and symptoms were

relieved by the administration of silver nitrate pills and opium. The second case (Stewart, 1889) was that of a man, aged thirty-nine, who for eight years had suffered from tetany. Stewart stated: "During the intervals of freedom from attacks he suffered from diarrhea which moderates when the tetany makes its appearance." Howard (1906) reported nine cases of tetany, one of which was associated with diarrhea. The patient was a man aged twenty-four, who had acquired the intestinal disorder while in the South. Howard stated that this was the only report of tetany in the adult of purely intestinal origin which had appeared in American literature for a decade. He cited two cases of tetany caused by gastroenteritis (Strong 1902, and Brown 1902) and mentioned iRegel's report of tetany associated with helminthiasis. In the British literature of the period, one finds a report by Thomson (1904) of a case of chronic pulmonary tuberculosis and marked "mucomembranous colitis" in which tetany developed with the patient was under his care. The patient recovered ultimately from both colitis and tetany.

The association of tetany with sprue, first recorded by Bassett-Smith (1910) is the first instance we have been able to find in which tetany was definitely connected with a particular type of intestinal disorder in the adult. Bovaird (1921) reported a series of thirteen cases of sprue with two of which tetany was associated. Barach and Murray (1920) reported one of Bovaird's cases in greater detail, giving figures for the blood calcium. In this case, which was typical of severe sprue, the blood calcium was 6.5 mg.

for each 100 c.c. and curiously enough was not elevated by intravenous calcium medication. Scott (1925) stated that low "ionic" calcium was a constant accompaniment of sprue, and mentioned the occurrence of tetany in severe cases. His patients showed little or no reduction in the total blood calcium; however, the method he used for the determination of ionic calcium, that of Vines, has not been generally accepted.

Among the other reported cases of diarrhea associated with tetany are those of Gibson (1923), Tileston and Underhill (1923), and Siffredi and de Rabinovich (1925). In both of the latter cases calcium studies were made; in Tileston's case fatty diarrhea had existed for six months associated with typical tetany and blood calcium of 6 mg. The cause of the diarrhea was not determined; metabolic studies, however, showed a tendency to calcium retention, excessive excretion of ammonia without other evidence of acidosis, and poor utilization of fat. In Siffredi and de Rabinovich's case the blood calcium was 8.3 mg. and the intravenous administration of calcium chloride promptly relieved the attacks of tetany. Among the most extraordinary cases of the kind on record are those of Blumgart, who described three patients suffering from asthenia, diarrhea, and anemia, one of whom died after an attack of tetany, the blood calcium being 5.3 mg. for each 100 c.c. The chief clinical and pathologic finding in Blumgart's cases was the malabsorption of fat; the small intestine was covered with punctate grayish elevations which histologically

showed collections of phagocytes loaded with fat.

The association of tetany and diarrhea in infants is much more common and since, in our case, there was evidence of gastro-intestinal disturbances dating from childhood, it is interesting to note the recorded cases. Langmead (1911) described fourteen cases of "relapsing tetany" associated with dilatation of the colon and abnormal and offensive bowel movements. These cases all occurred in children and in describing the patients he says, "The general growth and development was always retarded, the patients being thin, wizened and undersized." He comments on the resemblance of these cases to the cases described by Herter. Lichtenstein described the stunting of growth and physical retardation occurring in celiac disease; in four of his nine cases actual tetany was also present. It is not definitely known how late into adult life such intestinal disorders may persist (probably only until puberty) but a case described by Findlay and Sharpe suggests a relationship between celiac disease in infancy and tetany in the adult. They recount the case of a young woman who had suffered from celiac disease in infancy in whom recurring diarrhea developed in later life, and who subsequently had tetany. She had always been undernourished and underdeveloped, her maximal weight being six stone (84 pounds). The striking similarity to our case is apparent; Tileston and his associates also state that the case they reported was essentially a duplicate of that reported by Findlay and Sharpe.

The infrequent incidence of tetany in association with the relatively common symptom of diarrhea points to the possible existence of a predisposing cause. While tetany has been described as a complication of certain infectious diseases (notably typhoid fever and cholera) it is apparently rare in bacillary dysentery and amebiasis. Logan and Barger in their extensive experience with chronic ulcerative colitis have only observed one case associated with tetany. There have been cases reported under the indefinite diagnosis of "gastro-enteritis," and Loeper and Béchamp have found a low calcium content of the blood in this condition. Nevertheless, many of the reported cases in which diarrhea and tetany were associated have been complicated by constitutional or nutritional defect. The present knowledge of nutritional disorders and disturbances of the glands of internal secretion is too fragmentary to justify extensive hypotheses with regard to these defects, although the evidence bearing on their relation to tetany is of considerable significance. The common factors in the group of cases in which tetany and diarrhea are associated seem to be: (1) malnutrition and physical retardation, (2) recurrent diarrhea associated with deficient fat utilization, and (3) disturbance in calcium metabolism. The coexistence of these factors suggest at once either sprue or intestinal infantilism (Heubner's "schwere Verdauungsinsuffizienz"). As we have stated, our case presented such striking evidence of retarded development as to raise the question of pancreatic or intestinal in-

fantilism. These rare conditions are differentiated only with difficulty, and will probably remain unclassified until methods of studying pancreatic and intestinal digestive functions are perfected. Bramwell first described the pancreatic variety, and since then cases have been recorded by Rentoul, Clarke and Hadfield and others. Necropsy in Clarke and Hadfield's case showed an atrophic pancreas and chronic inflammatory changes in the colon. In none of the recorded cases was tetany associated. Herter (1908) described "intestinal infantilism," the clinical features of which are similar to those of celiac disease; in fact, Miller is inclined to regard both pancreatic and intestinal infantilism as varieties of the latter disorder. Strauch's description is excellent and applies to the entire group; "The principal factor is a very severe chronic intestinal insufficiency with much reduced function of the digestive glands, which is rather refractory to treatment and as a rule affecting children beyond the stage of infancy. The tolerance for fats and carbohydrates is reduced so that slight dietary indiscretion or a minor parenteral infection brings on a digestive disturbance of severe nature with marked loss of body weight and a reparability of function far below normal. But also without such recognizable causes obstinately relapsing diarrhea of a fermentative character will occur. In addition, or rather as a consequence of this, the somatic development becomes seriously impaired and finally the children are set back in body weight and height by years."

The occurrence of tetany in celiac

disease has already been mentioned (Lichtenstein), and its possible relation to tetany in the adult recorded (Findlay and Sharpe). In a recent review of Levinsohn, the increased loss of calcium in celiac disease is discussed; this is explained on the basis of either increased excretion or failure of resorption. He refers to the frequent association of tetany, which he regards as of the parathyroprivic type; necropsy reports describing atrophy and fatty degeneration of the digestive and endocrine glands are also cited. It therefore appears that either celiac disease or certain closely related conditions may be a factor in producing infantilism, fermentative diarrhea and constitutional defects, thus furnishing a possible background for tetany in later life.

Since sprue is the diarrheal disease of adults in which abnormal calcium metabolism and tetany occur most frequently, it is of interest to note the hypothesis of its etiology advanced by recognized authorities on the subject. Ashford regards physiologic glandular deficiency as one of the antecedent causes, stating that this deficiency involves the digestive glands and the glands of internal secretion. He also describes the symptoms of the condition, mentioning loss of weight, asthenia, constipation alternating with soft fermented stools, pigmentation of the face, vague myalgia, cramps in the limbs, and psychic irritability. The low blood calcium values noted in sprue have already been mentioned; Ashford and Hernández find that the blood calcium is below the normal level in sprue and in the nutritional disturb-

ances which constitute its major predisposing cause.

These observations on sprue furnish an interesting sidelight on the relation of tetany to diarrhea, and raise the question of whether our case and certain of the other recorded cases of colonic tetany were not actually sprue. The question unfortunately cannot be answered positively; Blumgart did not believe that his patient suffered from sprue, and in our case the diagnosis could not be established, in view of the patient's lifelong residence in the North and the absence of Monilia from the stools.

It must be remembered that certain obscure forms of tetany are on record in which there is evidence to show that parathyroid deficiency is present as a part of generalized endocrinopathy. In such persons, a variety of circumstances might precipitate an attack of tetany. Morawitz describes a boy of seventeen with infantilism, delayed growth of bone, and swelling of the salivary glands, who developed tetany after a fall at the age of seven. Woltman, in his discussion of a case of tetany in a eunuch with signs of polyglandular disease, mentions the theories of Falta and Weisel; they refer to multiple endocrine sclerosis due to a connective-tissue diathesis, as an expression of a generalized constitutional defect. Whether our patient suffered from a generalized endocrine defect, intestinal infantilism, or atypical sprue cannot be decided definitely without further observation and improved methods of study. It is of interest to note that probably latent tetany had been present for years (the

carpal spasms during pregnancy are suggestive of this), and that other evidences of endocrine disease were present as well.

Much experimental work has been done on the relation of the intestinal tract to tetany, the greater part of it having a direct bearing on the cases under discussion. The numerous studies on calcium metabolism in rickets with relation to diet, fats, fat-soluble vitamins, and the reaction of the intestinal contents are noteworthy and illustrate the difficulty of studying this problem. In most cases the clinical association of tetany and diarrhea depends, as we have stated, on disturbed calcium metabolism. Barach and Murray, in explaining the occurrence of tetany in sprue, state that the phenomenon depends on deficient calcium absorption, as well as increased calcium excretion through the colon; they cite von Noorden's view, that calcium is absorbed in the upper part of the intestine chiefly as the soaps of fatty acids, and therefore believe that calcium absorption must be interfered with in sprue, since this disease is associated with defective utilization of fat. This explanation would seem to hold also for intestinal infantilism. Holt, Courtney, and Fales have reported on the relation of fat in the diet to calcium absorption in children; they find a very low degree of calcium utilization in diarrhea and in chronic intestinal indigestion.

Dragstedt and Peacock studied the influence of diet in thyroparathyroidectomized dogs, and found that diets rich in lactose and dextrans prevented tetany, while meat diets precipitated at-

tacks; constipation also brought on tetany. Swingle and Wenner, in discussing the effect of the feeding of strontium in preventing tetany, stated that dietary factors, strontium administration, magnesium lactate and intravenous Ringer's solution prevent tetany by reducing the permeability of the intestine to calcium, and thus prevent loss of calcium through the colon. They believe that constipation and meat diets cause an increase of certain unnamed end-products of protein metabolism, which increase the permeability of the intestinal wall, causing increased calcium excretion and subsequently tetany.

Even more important observations on the relation of tetany and diarrhea are those of Luckhardt and Compere, who have shown that thyroparathyroidectomized dogs who have been kept free from tetany by the administration of calcium, can be thrown into tetany by drastic purgatives; these results are also explained on the basis of increased permeability of the intestine to calcium. Stewart and Percival, in their recent experiments, seem to furnish conclusive proof that the large intestine is the main excretory route for calcium, a point which further emphasizes the etiologic importance of diarrhea in the production of tetany. The occurrence of tetany in diarrhea, therefore, may be due to deficient calcium absorption, dependent on partial failure to utilize fat, or too rapid acceleration of the intestinal contents; probably both factors are important. There is possibly also increased calcium excretion through the colon due to changes in permeability. This relatively simple



explanation, however, probably does not account for all cases of intestinal tetany; factors such as the diffusibility of calcium, and its relation to other inorganic salts in the blood and tissues may be of fundamental importance. A case now under the care of Logan and Bergen illustrates how much is yet to be learned of the chemistry and physiology of tetany. In this case, in which colectomy and ileostomy have been performed for severe chronic ulcerative colitis, typical tetany develops without any change in the blood calcium, in consequence of obstruction to, or profuse discharge from, the ileostomy opening. In this case the relation of the intestinal tract to the production of tetany is very different from that in the case we are reporting. It emphasizes the possible variations and difficulties in the explanation of the problem. A study of this case now in progress may cast much additional light on the whole subject.

The introduction of parathormone by Collip has furnished the medical profession with a substance to control maternal, postoperative, and infantile tetany by its effect on the blood calcium. Its use has been reported in the treatment of sprue; in this disease Ashford and Hernández find that it elevates the blood calcium and controls the muscular "cramps," thus proving the latter to be a manifestation of latent tetany. These writers regard parathormone as an important adjunct to the dietary treatment of the disease, rather than a curative measure. Baumgartner also reports elevation of blood calcium in sprue after the use of parathormone but raises the question of

its possible effect on calcium reserve. In our patient there was marked general improvement (possibly due to dietary factors), relief from tetany, and a definite effect on the blood calcium. Although a high-protein diet and an attack of diarrhea lowered the blood calcium slightly in spite of parathormone administration, the tetany level of blood calcium was not reached, and the patient had no noteworthy symptoms. Figure 1 shows the blood calcium and phosphate levels during the period of observation with reference to diet and the medication employed.

The method by which parathormone acts on calcium metabolism is still under discussion. The experiments of Stewart and Percival indicate that this substance does not affect the rate of calcium absorption from the intestine, nor the rate of calcium excretion from the colon. It is probable, therefore, that the use of parathyroid hormone in colonic tetany is symptomatic treatment, and that attention to the underlying nutritional and constitutional defect is of primary importance. However, in our case it was impossible to accomplish anything until the tetany was under absolute control, and in this connection parathormone was invaluable.

There are numerous hypotheses with regard to the effect of parathormone on the calcium of the blood serum; Cantarow, Caven and Gordon believe that it acts by retarding the precipitation of calcium from the blood (that is, in osseous tissue) and by actual abstraction of calcium from the skeleton. Stewart and Percival suggest that the parathyroid hormone con-

trols the distribution of calcium between the blood and the tissues, by regulating the proportion of total serum calcium which is readily diffusible. Greenwald and Gross believe that the parathyroid hormone is the substance which keeps in solution the excess of

wald and Gross and those of Hunter and Aub established this point definitely. It must be appreciated, therefore, as has been pointed out by Greenwald and Gross, and others, that the use of parathormone does not improve calcium assimilation but rather causes

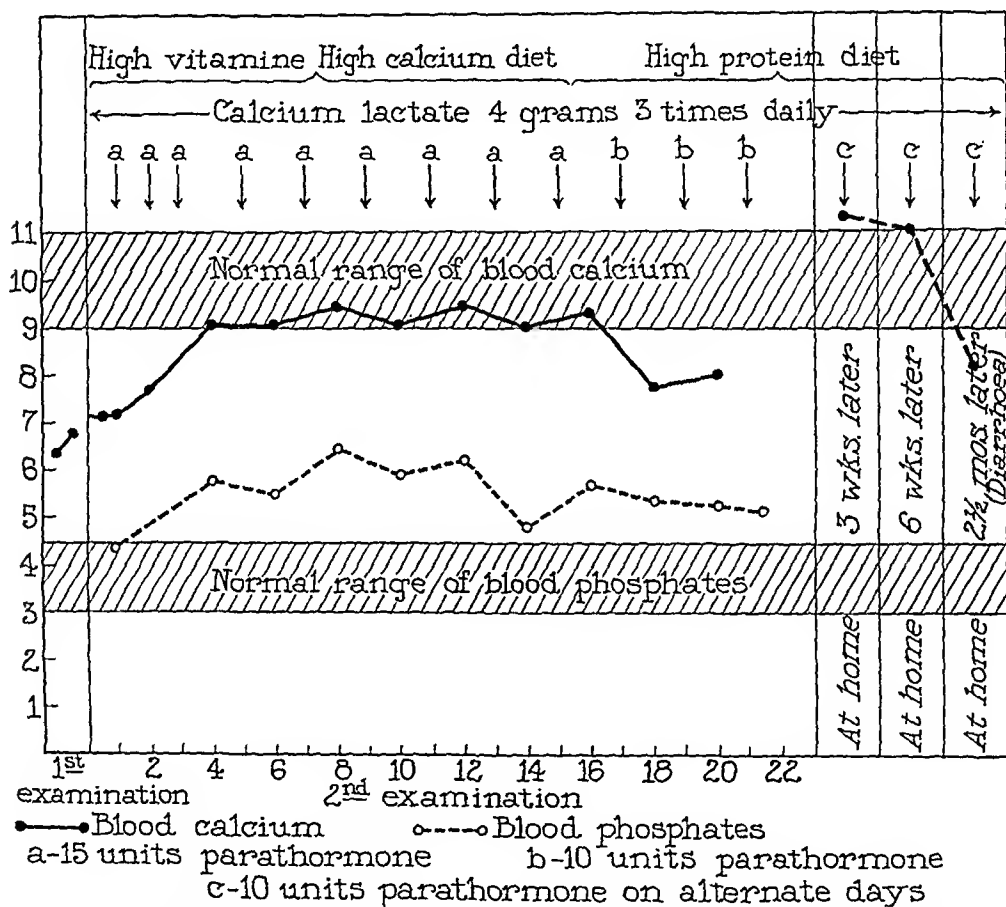


FIG. 1. The effect of treatment with parathormone and calcium lactate on the calcium of the blood serum in a patient with tetany due to chronic diarrhea.

calcium phosphate which Holt, LaMer, and Chown have shown to be present in the blood; or the hormone may be necessary for the preparation of this substance. It is generally agreed that the elevation of serum calcium produced by parathormone is brought about by the loss of calcium from the skeleton. The experiments of Green-

wald and Gross and those of Hunter and Aub established this point definitely. It must be appreciated, therefore, as has been pointed out by Greenwald and Gross, and others, that the use of parathormone does not improve calcium assimilation but rather causes

cial effects of sunlight and ultraviolet irradiation on calcium absorption.

### SUMMARY

A case of tetany due to diarrhea of obscure origin with nutritional and constitutional defects is described. The occurrence of related cases in the literature and the possible relation of this syndrome to sprue and intestinal infantilism is considered. The experimental evidence showing the relation

of the intestinal tract to tetany, and the possible influence of altered intestinal permeability on calcium absorption and excretion is discussed.

The therapeutic response in this case to the administration of parathormone and calcium lactate was striking, as shown by symptomatic improvement and by the behavior of the serum calcium. In view of the possible calcium depletion by parathormone, the necessity of adjuvant measures to protect the calcium reserve is emphasized.

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# The Significance of Ureteral Stricture in Relation to Abdominal and Other Symptoms

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STRICTURES of the ureters have been known to the urologist since the early days of ureteral catheterization. In 1902 Howard Kelly expressed the conviction that stricture of the ureter was a very real entity, often leading to mistaken diagnoses and an erroneous conception of the etiology of some renal diseases. It remained for Hunner to prove in them a source of trouble, often quite remote from the lesions per se, hitherto ascribed to disorder or pathology of other structures. Why the ureter, an essential unit in the body's drainage system, lined with a sensitive mucosa and highly vascularized, 30 cm. in length and subject to pressure, distortion, injury, as well as the constant possibility of conducting and being infected by material from the kidney or bladder, has escaped more careful scrutiny, is an unanswered question, and a challenge to clinician and urologist alike. It has not been an easy matter to establish in the medical mind the far reaching importance of stricture as the point of origin of so diversified a symptom-complex as is often easily proved to exist by the measure of relief which

so frequently follows appropriate treatment of the narrowed area. The effects of kinks and ptoses while often causative of similar manifestations should not be considered in this connection.

Women are apparently more frequently affected than men although it is possible that with increasing knowledge the disproportion in incidence may be less striking. The relative number of male and female patients which make up the clientele of each individual observer must also be taken into account.

Pathological investigations have furnished ample support for the establishment of ureteral stricture as an entity. Howard and LeCocq examined the ureters at fifty routine autopsies and found stricture and ureteritis to be extremely common. Eisendrath, Goldstein, Hunner and others have added records of gross and microscopic studies which are most convincing.

Strictures are caused by congenital and acquired influences. The latter group comprises by far the larger number and two main factors—focal infection and traumatism—are the pre-eminent causes. Foci of infection any-

where in the body, but especially those so commonly found about the head, may safely be assigned a major role. Other infections, of seeming local significance only, must also be reckoned with as possible etiologic factors. The infectious diseases are undoubtedly causative of narrowing at times, as proved, or at least very cogently suggested by a history of disturbance, perhaps of intermittent manifestation, occurring in the years which follow. Periureteritis with infiltration of the ureteral wall may follow or occur coincidentally with inflammatory processes in the immediate vicinity of the ureter. Penetrating injuries of the abdomen, by anyone of several agents, or traumatism resulting from operative procedures, wherein the operative field includes or lies in close proximity to the ureter, may serve as causes of obstruction, partial or complete, depending upon the extent of the injury. Hunner cites a group of cases occurring as sequelae to the reactionary inflammation incidental to the use of the cautery and radium in the treatment of pelvic neoplasms.

The symptomatology in one group of cases directs attention at once to the kidney-ureter-bladder tract, the manifestations being those of renal or ureteral colic. Sudden occlusion from edema of the strictured area is the probable explanation for the appearance of such attacks. Such cases are likely to receive the benefits of early catheter investigation, but unless the possibility of stricture plus edema is borne in mind as a cause, a report of essentially negative findings may be returned. In any case the dilatation

incidental to the catheterization often brings the desired relief. In another and much larger group the symptomatology is often most diversified and without painstaking study may appear to bear no relationship to the urinary tract. It is usually possible to elicit some complaint, often considered by the patient as a very minor or inconsequential phase of his ailment, which is subjectively related to the bladder. The most frequent symptom is frequency of varying degree; again dysuria mild or severe or a combination of the two. Frequency is often alleged to be a direct result of nervousness, but by and large, individuals with a normal urinary tract do not so react when under the influence of nervous strain. Dysuria, when present, varies in degree from a slight burning, often hardly sufficient to attract attention, to actual pain. Incontinence has been reported as an outstanding symptom in some instances: in our series three patients complained of a definite lack of control. In this connection we are impressed with the belief that the prolonged incontinence often seen in childhood may, in at least a portion of the instances, be dependent upon an unrecognized or unsuspected ureteral stricture. Any or all of these symptoms may result from a cystocele with its attendant cystitis and this fact must be taken into account in the making of a differential diagnosis. Moreover it must not be forgotten that the two conditions may exist coincidentally.

Painful coitus is a not infrequent complaint from which complete relief has been experienced in a number of instances by the dilatation of a stric-

ture at or near the pelvic brim. The rather close anatomic relationship between the upper third of the vagina and the lower ureter together with the changed conditions incidental to the act is the probable explanation for the pain. Abdominal manifestations varying from diffuse pains to symptoms referable to one or more of the contained viscera are frequently encountered. A chronic appendicitis is perhaps diagnosed in error more often than any other condition and it is safe to say that large numbers of appendices have been removed without relief of symptoms which were on the contrary due to a strictured ureter. It is quite possible that the appendix serves at times as a focus of infection which may be causative of ureteral pathology, but this, we believe, is infrequently the case. Physical evidence of gall bladder dysfunction or pathology has been observed to disappear entirely following the discovery and appropriate treatment of a right-sided stricture. This phenomenon has been so striking in its frequency of occurrence that we feel justified in recommending ureteral catheterization, especially an investigation of the right side, as a preliminary to operations upon the gall bladder. In many instances we have found pathology in both places and in several the lesions have been so sufficiently advanced that the correction of one would have rendered the patient a measure of benefit not at all commensurate with justifiable expectations. Gaseous distension of the hollow viscera and disturbed function of the colon, quite often diagnosed as a colitis, have in several instances been traced in the last analysis

to ureteral pathology. Extra-abdominal symptoms such as persistent headaches, thoracic pains of varying distribution, pains in the lower extremities, low grade temperatures, often of daily recurrence, peculiar mental reactions, etc., have been met with. The manifestations enumerated find their explanation in toxic and reflex influences. Evidences of a low grade nephritis, a result of back pressure and infection acting singly or in conjunction with each other, have been observed to disappear with the relief of stricture. A lack of endurance is an outstanding feature in practically all cases.

The disability which arises from this condition is often very great in proportion to the size of the lesion. Not infrequently one encounters a patient who in his search for health has not only been treated medically for years but quite often has undergone one or more laparotomies and all without benefit. Many have been classified as chronic neurasthenic invalids whilst others have been looked upon, especially by many physicians who have been years in practice, as nuisances or pests. One's faith in the virtues of the healing art becomes rehabilitated and refreshed when one of these patients, whose complaints have been legion, states without reservation that he is well.

The diagnosis is usually established from the history but often a most searching inquiry must be made into details, lest seemingly inconsequential or trivial symptoms are passed over as meaningless. The physical examination is in some instances most convincing in its pointings but on the



other hand it may yield little or nothing that is helpful. Painsstaking care is required in the evaluation of findings and the possibility of the existence of a stricture calling weakly for recognition must not be lost sight of when the findings seem vague and more or less obscure. Tenderness high in the kidney angle can usually be found but several instances have come to our attention in which it has not been present. Heavy percussion with the fist will occasionally bring it out when direct pressure fails. As the ureter crosses the pelvic brim between McBurney's point and the umbilicus, usually nearer to the latter, pressure at this point will usually call forth in stricture patients localized or referred pain. Occasionally a similarity to a distress included in the list of ailments will be recognized at once and commented upon. The discomfort may be referred upward to the epigastrium or to one or the other kidneys or downward to the bladder or to the vicinity of one or the other ovaries. A desire to void may be experienced and heed should be taken of this even though it is very slight. The point just mentioned may be the site of the maximum tenderness and pressure above or below this will evoke a discomfort of lessening intensity only. In the event that the appendix overlies or is fixed in close proximity to the ureter and is itself sensitive to pressure a fine discrimination will be required to separate the response from each structure, if it is at all possible to do so in an individual case. In women the bimanual examination of the pelvic structures is relatively easy and the lower

ureteral zone—not the ureter per se—can be readily palpated. Again, pain or discomfort may be referred to any part of the kidney—ureter—bladder tract. Attention should be directed to the fact that the ureter lies in close proximity to the anterior aspect of the sacro-iliac joint at and just below the pelvic brim and pressure at this point may call forth pain from an arthritis rather than from stricture. Examination of the back should also be made to prevent this error, bearing in mind that the two conditions may co-exist.

It is quite natural to assume that the examination of the urine should disclose information of value; in a portion of the cases this is true while in the great majority the findings are either of a quasi-suggestive nature or entirely negative. Hunner's statement in respect to this phase of the examination is quite comprehensive in its details—"In 20 per cent of stricture patients, there is a chronic pyelitis on one or both sides, and the urine will give characteristic findings. In 50 per cent only a few erythrocytes, a few leukocytes, albumin from a slight trace to large quantity, or casts, or a combination of these elements will be found. Too often in the past such evidences of disease, when found in meager quantity and only on the most painsstaking urinalyses, have been considered as of no significance. In the remaining 30 per cent of stricture cases, the urinalysis is completely negative and patients in this group may present symptoms strongly pointing to the urinary tract and yet be sent to the gastro-enterologist, the orthopedist, or the explor-

tory laparotomist for a diagnosis simply because of the negative urinalysis." To this should be added, that in the female especially, deductions should be made from the examination of catheterized specimens only. The reason for this is obviously to eliminate a vaginal or urethral source of contamination.

The *modus operandi* by which stricture damage is wrought can be briefly stated and readily visualized by the following statement of the sequence of events, viz. obstruction, stasis, infection, back-pressure. It is at once apparent, therefore, that a narrowing of the ureter constitutes a violation of a fundamental principle—the maintenance of free drainage. The deleterious effects which may be ascribed to this particular disturbance in function have been clearly and concisely set forth by Hunner in the following paragraph. "The more common renal diseases which in large measure may be traced back to the injury caused by ureteral stricture are hydronephrosis (sterile or infected), chronic pyelitis and pyonephrosis, pyelitis of the pregnant and puerperal periods, chronic pyelitis in children, renal and ureteral calculi, the renal inflammatory processes resulting in the so-called essential hematurias, and the various pathological processes which drive to the urologist the patient with congenital malformation of the upper tract. It is probable that many of the chronic nephritides resulting in multiple abortions are secondary to stricture, as are some of the chronic renal processes formerly considered as amenable only to medical methods of treatment."

The treatment of stricture comprises a diagnostic as well as a therapeutic phase. In the first premise the stricture is located and if passable its caliber determined, whilst in the second a therapeutic dilatation may be done. Urograms may or may not be made at this time depending upon the conditions encountered. It is important that visualization be done as early as practicable to the end that the type of stricture—single or multiple and the extent of ureteral wall involved—may be determined and information as to the condition of the renal pelvis be gained. In any case it is best to do one side at a time and not allow the patient to be ambulatory until the day following or until all pain has disappeared.

Ultimate success in the treatment of stricture per se depends upon the removal of foci of infection. The disposal of such areas eliminates further influence in the stricture zone and at the same time dispenses with possible deleterious effects in relation to other structures.

The number of dilatations in any given case will depend entirely upon the conditions encountered in that patient. As a rule the first two or three treatments, depending upon the temperament and reaction of the individual patient, should be received in the hospital while subsequent ones may be carried on in the urologist's office.

We have selected, from our series of about sixty cases, a few examples that will serve to illustrate some of the settings which have been dwelt upon in the text of this paper.

*Case I.* Mrs. T., age 46 years.

*Family, menstrual, marital and past histories: negative.*

*Present complaints:* Nervousness, ready fatigue, conscious irregularity of heart's action, breathlessness on exertion, intermittent annoyance and distress in epigastrium attended by pyrosis and gas after food, intermittent frequency.

*Examination:* Thyroid adenoma (moderately toxic), tachycardia (moderate), multiple extrasystoles, hypertension (moderate), physical evidences of gall bladder pathology, tenderness (sharp) in right kidney angle. Gastro-intestinal x-ray study negative. Radiography of gall bladder region revealed a constant solitary shadow.

*Treatment outlined:* a. ureteral catheterization; b. cholelithotomy, possible cholecystectomy with appendectomy; c. removal of thyroid adenoma.

*Ureteral catheterization:* Left normal. Right impassable at pelvic brim but bouginage succeeded after 3 or 4 trials with release of purulent colon-infected urine.

*Diagnosis—urological:* Stricture, hydro-pyonephrosis.

*Treatment—urological:* Dilatation at intervals with resulting relief of infection and restoration of practically normal kidney function.

*Comment:* The strictured ureter constituted symptomatically a seemingly minor part in this clinical picture. Relief of all other conditions and failure to have discovered this would have left this woman to face destruction of the right kidney with its train of evil consequences.

*Case II.* Mr. H. W. P., age 29 years.

*Family, venereal and marital histories: negative.*

*Past history:* Mumps, measles, a few sore throats, an average number of colds.

*Present complaints:* Four or five years ago a low grade, more or less constant "pressure pain" appeared in the right in-

guinal region; no complements, such as nausea or cramps are recalled. A chronic appendix was diagnosed and an appendectomy done; relief has not followed, on the contrary he is worse than before. Three third molars were removed two years ago without benefit. Gastro-intestinal studies and a cholecystography were done; the findings were said to disclose nothing distinctive, but questionable features in the history, led to the institution of an ulcer regime which was carried on for a year without improvement. During this period he had an attack of abdominal pain described as very severe and characterized by sudden onset; this was ascribed to too much laxative powder. At present—June, 1927—has an "old-fashioned stomach-ache" most of the time. There is more or less nausea and at intervals the abdomen is diffusely sensitive to touch. Attacks of generalized abdominal cramps followed by diarrhea of several days' duration occur not infrequently, the loose stools often contain much stringy mucus. Cramps frequently waken him in the morning. An abundance of gas with associated pyrosis and not related to the taking of food is common. Patient alleges that he has but little "pep" and less endurance; he may rest well at night, at times, and waken feeling well, but within a couple of hours be overtaken by a sensation of great fatigue. Under such conditions his color on rising has been observed to be good, but when the sense of exhaustion comes over him he will become pale and show dark circles under the eyes. He is nervous, irritable, easily annoyed and worried about his health and incidentally about his position because of lessening efficiency. There are no kidney-ureter-bladder tract symptoms.

*Examination:* Complexion muddy; fine tremor of extended hands; an intra-nasal contact interfering with drainage; a mild naso-pharyngitis; tonsils atrophic but show many retaining crypts, some of which are occluded; generalized abdominal tenderness with localized increase in the gall bladder area and on either side of and in close proximity to the umbilicus—no radiation noted;

sharp and well localized tenderness in both kidney angles; lower pole of right kidney felt on deep inspiration and slightly tender. Three urinalyses were done, one was entirely negative, the other two chemically negative, but the sediment in one showed a few pus cells and in the other an occasional pus clump.

*Treatment outlined:* Preliminary investigation of the K-U-B tract, further steps to be determined later; dietary regulation when all studies have been completed.

*Ureteral catheterization:* Bladder normal. No. 6 catheter obstructed at 4 cm. on right side; this was replaced by a No. 5 which passed the initial obstruction but was hindered in its further passage at 20 cm. On the left side a No. 6 passed readily into the pelvis. Differential function, appearance time of dye on right side 4 minutes, from left side  $7\frac{1}{2}$  minutes. Urograms were made.

*Diagnosis—urological:* Multiple strictures of the right ureter with a moderate hydronephrosis; probable stricture of the left ureter as visualized in urogram. No infection.

*Treatment—urological:* Dilatation of strictures at appropriate intervals, the latter to be determined by response.

*Comment:* This young man had passed through the hands of five or six of the outstanding physicians in this community and failing to get results had quite naturally become very skeptical. He submitted to the procedure outlined after due deliberation and when he was discharged from the hospital he stated to the Interns that he was free of pain for the first time in four years. Consent was given for a tonsillectomy but he demurred as to further x-ray studies, etc., alleging that he had had repeated observations of this sort without relief, but agreed that he would again submit if no improvement followed the ureteral catheterization.

September 27—'27. Three ureteral dilatations have been received and a tonsillectomy has been done. He reports that, aside

from some trouble with increased intestinal gas following such foods as cabbage and cauliflower, he is well. He stresses the fact that his mind is more clear and that he is not nervous. Conscious heart's action of which he formerly complained has practically disappeared; his endurance has improved and he awakens refreshed in the mornings. Examination of the abdomen reveals much less tenderness and no suggestion of localization as previously mentioned. There has been a gain of 10 pounds in weight.

This patient is being seen at intervals and returns voluntarily for an occasional ureteral dilatation. His condition continues good and we can only conclude that the ureteral pathology has been in large part if not entirely responsible for his prolonged disability.

*Case III.* Mrs. A. M. P., age 40 years.

*Family history:* Negative.

*Menstrual history:* Periods always painful and very irregular, especially of late.

*Marital history:* Married at 17; divorced and history suggests that patient contracted a gonorrheal infection. Remarried; no pregnancies, no prevention practiced.

*Past history:* Rubella, parotitis, pertussis, diphtheria—a protracted ear complication followed the latter—, frequent colds, many attacks of tonsillitis.

A nervous complaining child, in fact has not changed to the present time. Stomach upsets and cramps frequent, usually ill two or three days each week.

Mild rheumatic joints for many years, relieved in great part by tonsillectomy.

Has had three laparotomies—an appendectomy, a partial oophorectomy, later—she was told—a total oophorectomy, but this was in error as she still menstruates.

*Present complaints:* Nervousness, irritability, despondency, frequent weeping often without provocation, easy fatigue, sleep not restful or refreshing, nocturia—2 or 3 times—headaches, often attended by nausea and vomiting—has vomited after each meal for



FIG. 1. Case 2. H. W. P. Bilateral Pyelograms. Stricture locations: Left uretero-pelvic junction. Right upper ureter.

several days at a time—, much gas after food, frequent pyrosis, constipation, head pains in various locations and always made worse by excitement and disagreeable circumstances—pains are usually worse at night and in the early morning—, occasional precordial and frequent severe diffuse abdominal pains. Weight increased between the ages of 25 and 30 and has not declined despite the disturbances cited.

*Examination:* A healthy appearing, somewhat overnourished woman; weight 158 pounds; height 5'5"; three devitalized teeth—radiographically negative—, mammae very sensitive to touch; gall bladder reacts sharply to all physical maneuvers; moderate diffuse abdominal tenderness—sharp localization about laparotomy scar, not possible to establish relationship of tenderness to any definite underlying structure—; tenderness in both kidney angles; sharp tenderness over upper end of right sacro-iliac joint; remaining pelvic structures normally posed; marked diffuse bi-manual tenderness.

Catheterized urine showed albumin a slight trace, leucocytes and a few pus clumps, a few calcium oxalate crystals.

*Treatment outlined:* Investigation of K-U-B tract first. Subsequent course to be worked out pending the results of this study.

*Ureteral catheterization:* Bladder mucosa paler than normal; ureteral orifices within range of normal. A No. 5 catheter obstructed 7 cm. above right orifice but finally passed to pelvis of kidney; abundant clear urine drained and following this 12 c.c. were withdrawn by light suction. On the left side a No. 5 catheter passed readily to the kidney; urine clear. Differential function, left kidney appearance time 2½ minutes, right 6 minutes. Urograms were made. Patient complained bitterly of pain at about the level of the obstruction in the right ureter when the iodide solution was being injected.

*Diagnosis—urological:* Stricture, first degree hydronephrosis, infection and slight nephroptosis on right side.

*Treatment—urological:* Dilatation of

stricture at suitable intervals with treatment of the infection.

*Comment:* This case appeared like a hopeless situation and an attitude of skepticism toward the procedures suggested was evident. Such an attitude has been engendered by years of disappointing medical and surgical treatment. Several months have elapsed and the patient has returned for treatment on four or five occasions; she has been carefully observed and attention given to devitalized teeth, the dietary, etc. She is taking no medicine and alleges that in the main she is well. The husband states without reservation that his wife has not been as well in years. In the beginning we entertained a reasonable doubt as to the reliability of the patient's glowing reports of relief, but at this time there is seemingly ample proof that the glamor of the initial benefit was real.

*Case IV.* Miss A. G., age 24 years.

*Family history:* Father died of brain tumor at age 57; otherwise negative.

*Menstrual history:* Periods always regular but painful, especially so in the past few months. Latterly all complaints are aggravated at the menstrual times and she shows a disposition to become hysterical.

*Past history:* Rubella, varicella, parotitis, scarlet fever—all without known sequelae. Frequent tonsillitis until tonsillectomy at age 19. A healthy child. In early adolescence began to be nervous; sick headaches (not menstrual) appeared, but have lessened in frequency in later years; began having nervous spells characterized by periods of exhaustion; a digestive disturbance of intermittent manifestation and apparently unrelated to the taking of food gradually developed and continues to the present time—has pyrosis, gas after food, occasional generalized abdominal cramps; soda occasionally relieves—. Patient does not smoke or use liquor.

*Present complaints:* Very nervous all of the time, irritable, restless, lack of endurance, inability to concentrate on her work because of periods of mental vagueness, noc-

turia—about 3 times—appeared about the same time as the digestive disturbance and like it is subject to remission, very sensitive to cold.

*Examination:* A rather frail young woman with an expression suggesting depression. Weight—net—115 pounds; height 5'8"—estimated. Complexion muddy; rather coarse but fairly rapid tremor of the extended hands; tongue tremulous and heavily coated; gall bladder reacts slightly to physical maneuvers; cecum partially filled and can be rolled under the finger; fairly well localized but moderate tenderness in vicinity of McBurney's point, also in the median line about  $1\frac{1}{2}$  inches below the umbilicus with radiation upward in the median line; well localized tenderness in the right kidney angle; pelvic negative.

Fractional gastric analysis disclosed a moderate hypoacidity. Gastro-intestinal study negative excepting a retention of barium in the appendix with tenderness on manipulation. The blood showed a moderate reduction in hemoglobin and total red count. Basal metabolic rate estimation gave a  $-2\%$ . Catheterized urine showed a few leucocytes in the sediment only.

*Treatment outlined:* Preliminary investigation of the K-U-B tract; possible appendectomy later; dietary regulation.

*Ureteral catheterization:* Bladder mucosa pale. A No. 6 catheter was obstructed in its passage at 20 cm. above the bladder and was replaced by a No. 5 which passed the narrowed area with difficulty. Another obstruction was met at the uretero-pelvic junction which was also passed with difficulty. On the left side a No. 6 passed readily to the kidney. Differential function, the appearance time on the right side was 12 minutes, on the left side 3 minutes. Urograms were made.

*Diagnosis—urological:* Double stricture of the right ureter. The one at the uretero-pelvic junction of the pipette type.

*Treatment—urological:* Dilatation of strictures at intervals.

*Comment:* This patient has been examined

in Europe and for the past three years has been under the care of the Staff in a large closed hospital. The only treatment prescribed in the latter institution was 2 grains of thyroid extract daily; the discontinuance of this lessened the nervousness definitely. An examination by a psychiatrist in Boston resulted in her being classified as a non-reader. Our study of the case led to the following beliefs: a. a possible slight thyroid hypofunction; b. ovarian dysfunction; c. a digestive disturbance of extra-gastric origin; d. moderate intestinal stasis; e. possible pathology along the kidney-ureter-bladder tract. The peculiar mental reaction could not be based upon any evident findings. The first ureteral catheterization was received in September and following this she returned to her studies in an eastern college. Reports were received that the quality of her work had improved, the digestive disturbance had been in abeyance, the nocturia had not returned, sleep was more refreshing and there was less nervousness. During the Christmas holidays she returned for further treatment. At this interview the patient added to the above that dizziness which formerly troubled her considerably had disappeared, the vague periods (mental) seemed less definite and that she is not quite so tired as has been her habit to be. An examination of the abdomen disclosed a total absence of all areas of tenderness.

We believe that the discovery of the strictures on this case was very timely and that the treatment given has had much to do with the improvement in her health. It is also our belief and hope that she will experience further benefits in the future.

Four other case protocols are included in this communication but are reported in less detail than the first four.

*Case V.* Mrs. E. R., age 35 years.

*Family, menstrual, marital and past histories:* negative.

*Present complaints:* Headaches, loss of weight, general weakness, constipation, frequency, pain in right kidney area, inability



FIG. 2. Case 4. Miss A. G. Right Pyeloureterogram. Stricture (pipette) at right ureteropelvic junction.



to carry on household duties because of lack of strength. Has received prolonged treatment directed toward the gastro-intestinal tract without notable benefit.

*Examination:* No disclosures were made that would explain the symptomatology. Catheterized urine showed a few pus clumps and a few leucocytes.

*Treatment outlined:* Initial study of the K-U-B tract; further investigations to await the outcome of this inquiry.

*Ureteral catheterization:* Bladder normal. Catheter obstructed at uretero-pelvic junction on right side. Drainage from right kidney scant and function decreased. Left normal. Urograms made.

*Diagnosis urological:* Tight stricture at uretero-pelvic junction; moderate hydronephrosis; definite loss of function.

*Treatment urological:* Dilatation of stricture zone at suitable intervals, drainage and lavage of renal pelvis.

*Comment:* This patient has been almost entirely relieved of the general symptoms of which she complained and experiences no further urinary tract annoyance. Dietary regulation is observed but no medicine is being taken.

*Case VI.* Baby G., age 3 years

*Family history:* negative

*Past history:* negative excepting an attack of measles nine months ago.

*Present complaints:* Weakness, anorexia, pallor, pain in the lower abdomen. All symptoms appeared following the attack of measles.

*Examination:* No noteworthy physical findings excepting an apparent loss of weight and diffuse tenderness over the lower abdomen. Blood Wassermann negative. Blood count showed a moderate secondary anemia. Preliminary urinalyses negative but later studies disclosed a few leucocytes only.

*Treatment outlined:* Cystoscopy, probable catheterization of the ureters; later procedures to be developed following this study.

*Ureteral catheterization:* A mild cystitis. Right ureter obstructed 9 cm. above the

bladder and the left 7 cm. above the bladder. Urograms were made.

*Diagnosis—urological:* Bilateral multiple strictures, hydroureter and hydronephrosis.

*Treatment—urological:* Dilatation of strictures at appropriate intervals.

*Comment:* We believe that the ureteral strictures were congenital in origin and the attack of rubella served to precipitate the symptoms. The immediate effect of the measles virus or other concomitant irritant was undoubtedly edema and this in turn increased the obstruction. This child has received two dilatations and appropriate tonic treatment; his condition is markedly improved in all respects.

*Case VII.* Mr. T. M., age 58 years.

*Family, venereal and marital histories:* negative.

*Past history:* Negative.

*Present complaints:* Gradually increasing frequency, weakness, lessened efficiency, loss of weight, anorexia, backache, digestive disturbance with tendency to constipation.

*Examination:* A somewhat undernourished tired-appearing man. A group of semipersistent râles in right apex. Colon moderately distended with gas and more or less sensitive over its course. Tenderness in the right kidney angle. A moderately enlarged prostate. Urinalysis disclosed a trace of albumin, a moderate pyuria.

*Treatment outlined:* Preliminary investigation of K-U-B tract. Other measures to be held in abeyance until this study has been completed.

*Ureteral catheterization:* Right ureter normal. The left ureter narrowed to small caliber at 7 cm. above the bladder and again at the uretero-pelvic junction. Urograms were made. Complete loss of function on the left side according to the dye test.

*Diagnosis urological:* Cystitis; enlarged prostate; residual urine, infected—amount 250 cc.; double stricture of left ureter with associated hydronephrosis (capacity of renal pelvis exceeds 6 cc.).



FIG. 3. Case 5. Mrs. E. R. Right pyelogram, and partial ureterogram. Suggests stricture at ureteropelvic junction and in lower ureter segment (catheter passed into ureter and turned upon itself, failing to pass lower stricture).

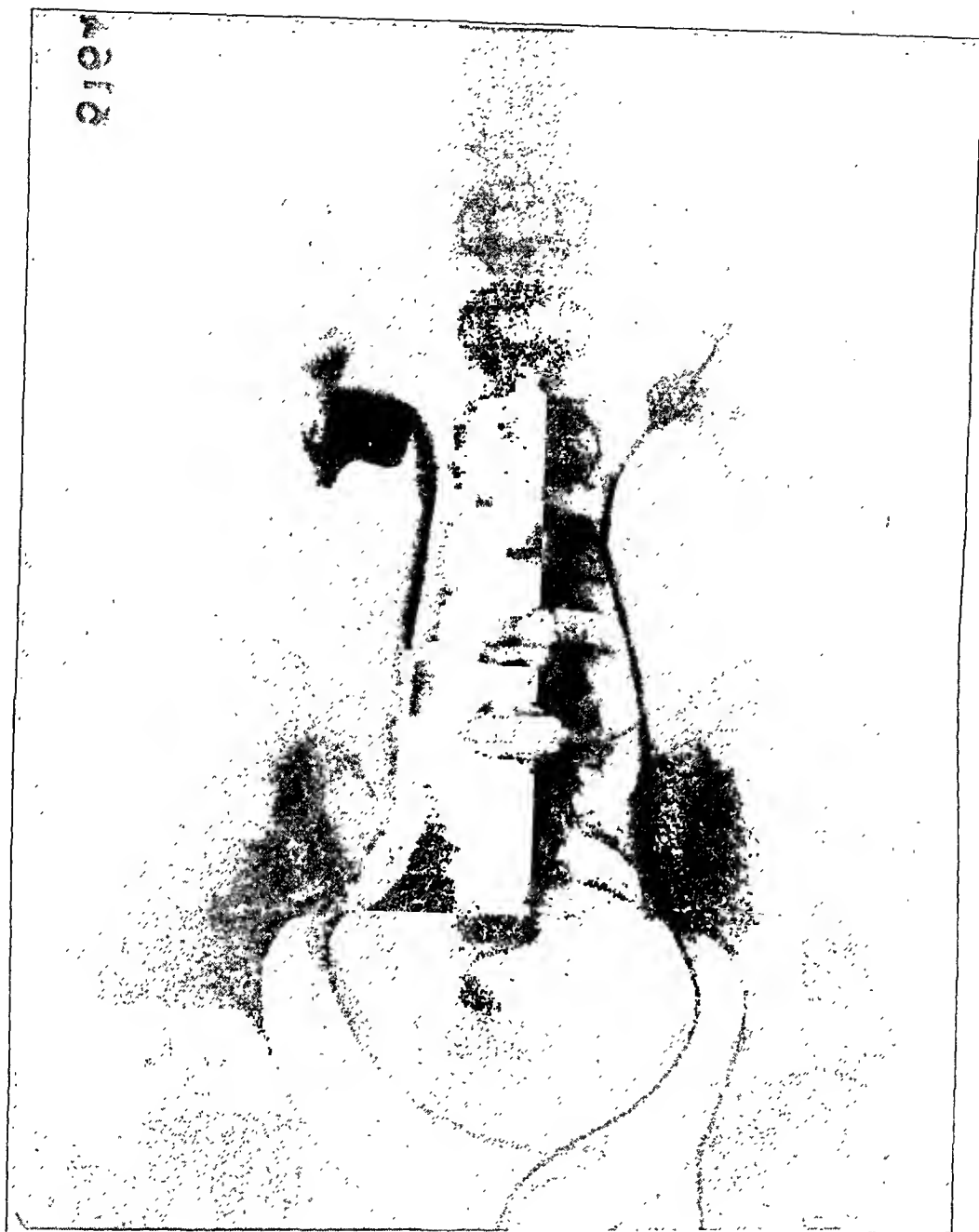


FIG. 4. Case 5. Mrs. E. R. Bilateral pyelograms. Stricture at ureteropelvic junction, both sides, with high insertion of ureter, on right side. Compare with Fig. 3, and note lessening of hydronephrosis. This study made after relief of symptoms.

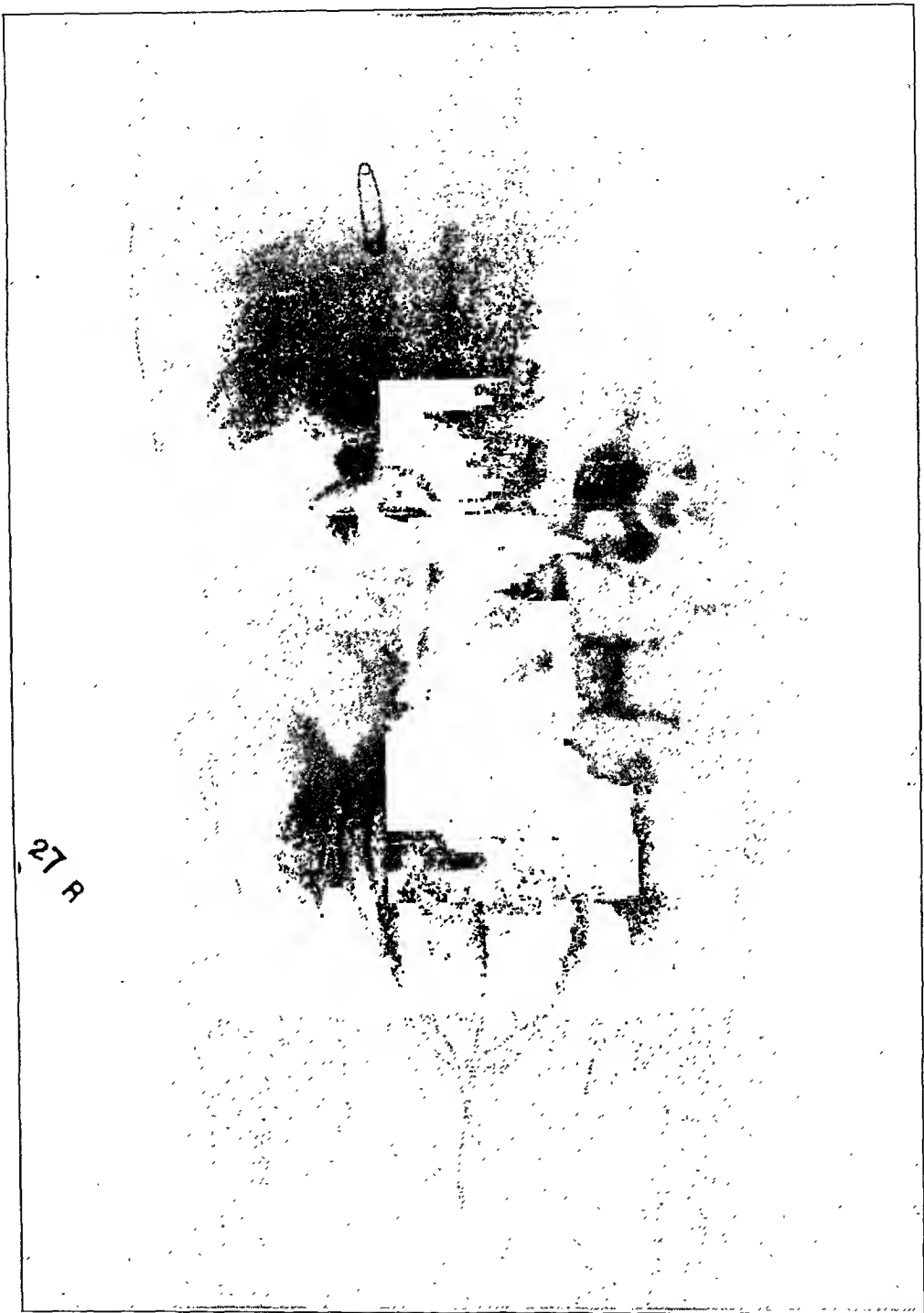


FIG. 5. Case 6. Baby G. Bilateral pyeloureterograms. Note pyelectasis and kinks and dilations of ureters. Bilateral strictures of midureters. See text.

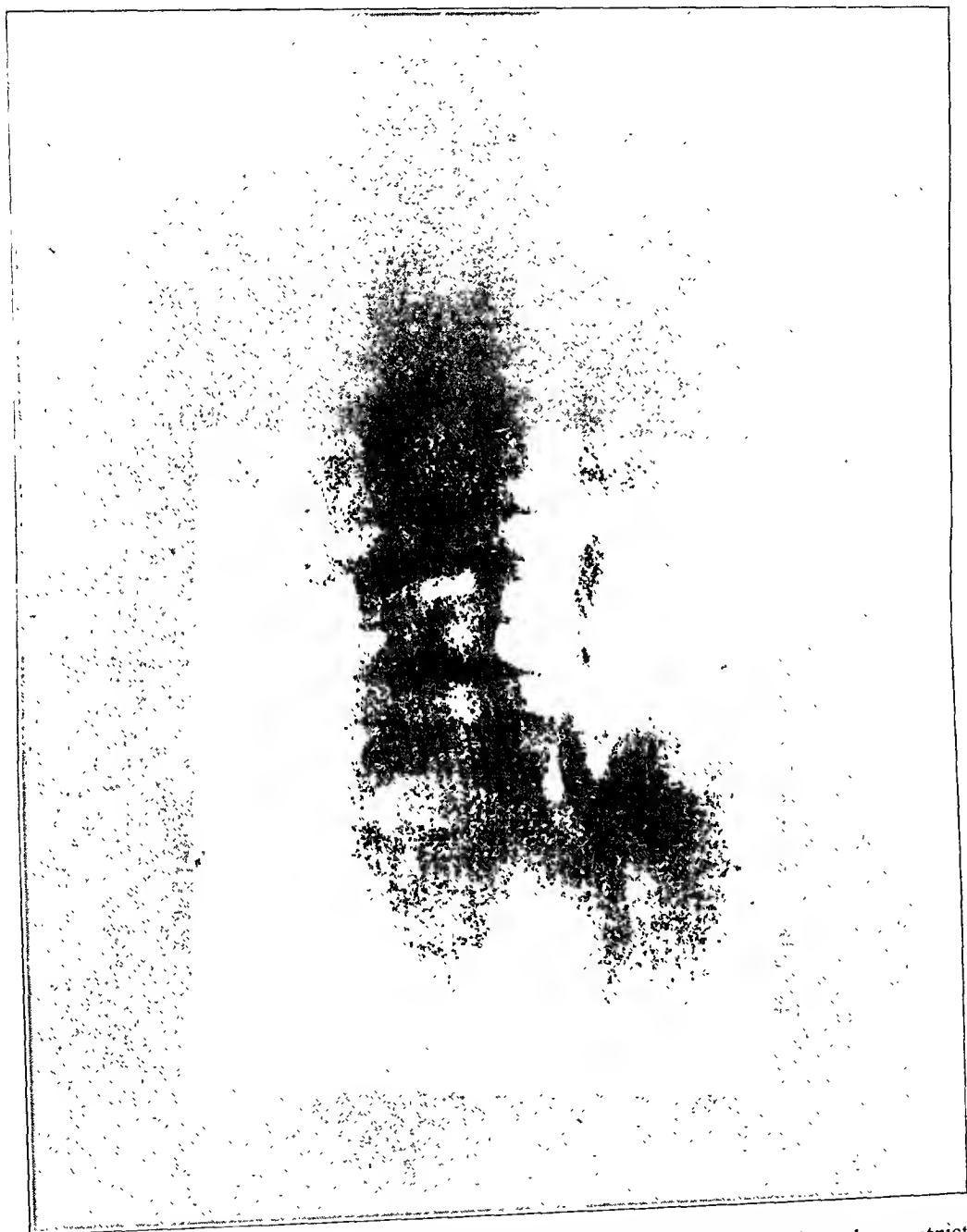


FIG. 6. Case 7. Mr. T. M. Left pyelogram. Marked hydronephrosis and two stricture areas, one near pelvis and one in m.d. portion of ureter. See text for notes on case.

*Treatment urological:* Appropriate treatment of cystitis; dilatation of strictured ureter with drainage and lavage of the renal pelvis at 30 to 90 day intervals; urinary antiseptics internally.

*Comment:* This patient has been under treatment for about one year. He has gained in weight and has been relieved of his backache since the first treatment. The left ureter is patent, the bladder function and the urine are normal. There has been an entire absence of symptoms for more than six months. The pulmonary condition has cleared—a relationship between the pulmonary findings and the infection along the urinary tract is not alleged but it is known that in generalized tuberculosis an active process along the intestinal or urinary tracts will keep a pulmonary lesion from becoming quiescent. No other treatment than that given with dietary regulation has been received. A former diagnosis of colitis, cystitis and possible pulmonary tuberculosis had been made.

*Case VIII.* Miss J. S., age 14 years.

*Family and menstrual histories:* Negative excepting as noted below.

*Past history:* Frequent attacks of tonsillitis. Tonsillectomy has been done.

*Present complaints:* Recurring attacks of pain in left flank, often accentuated during menstruation.

*Examination:* Well nourished but pasty looking girl. Physical examination otherwise negative excepting a slightly palpable and very tender left kidney. Tenderness in kidney angle sharp. Urinalysis: a trace of albumin, a few hyaline casts, an occasional leucocyte and erythrocyte.

*Treatment outlined:* Catheterization of left ureter.

*Ureteral catheterization:* Slight cystitis. Obstruction of left ureter at uretero-pelvic junction; following passage of impediment cloudy infected urine drained. Right side normal.

*Diagnosis—urological:* Stricture at uretero-pelvic junction with moderate hydro-nephrosis.

*Treatment—urological:* Dilatation of stricture at appropriate intervals.

*Comment:* The symptoms have been entirely relieved and the urine has returned to normal. This patient continues in apparent full health at the end of one year.

## SUMMARY

Eight cases have been reviewed. The results thus far justify reasonable enthusiasm but it must not be understood that the study has become a fetish and a hope established that a therapeutic path to Elysian fields has been discovered. On the contrary we have established, from our own studies as well as those of others, a firm conviction that there are a large number of people who are victims of this condition to whom benefit, such as has been described, might accrue if obscure situations with only suggestive symptoms could be intelligently and painstakingly investigated.

Our interest in this condition was very modestly aroused several years ago but not until the past year did we take up the study more intensively. Thus far we have collected sixty-two cases most of which have been brought to light in the latter period. In this group there have been many striking examples of sustained benefit, some who have reported improvement in some respects only and others in whom we have been frankly disappointed.

In this series there are 18 males and 44 females: the age variation has been from 3 years to 61 years: the largest number of cases was in the fourth and fifth decades. There were 31 patients with symptoms referable to the genito-urinary tract and 31 whose complaints bore no relation

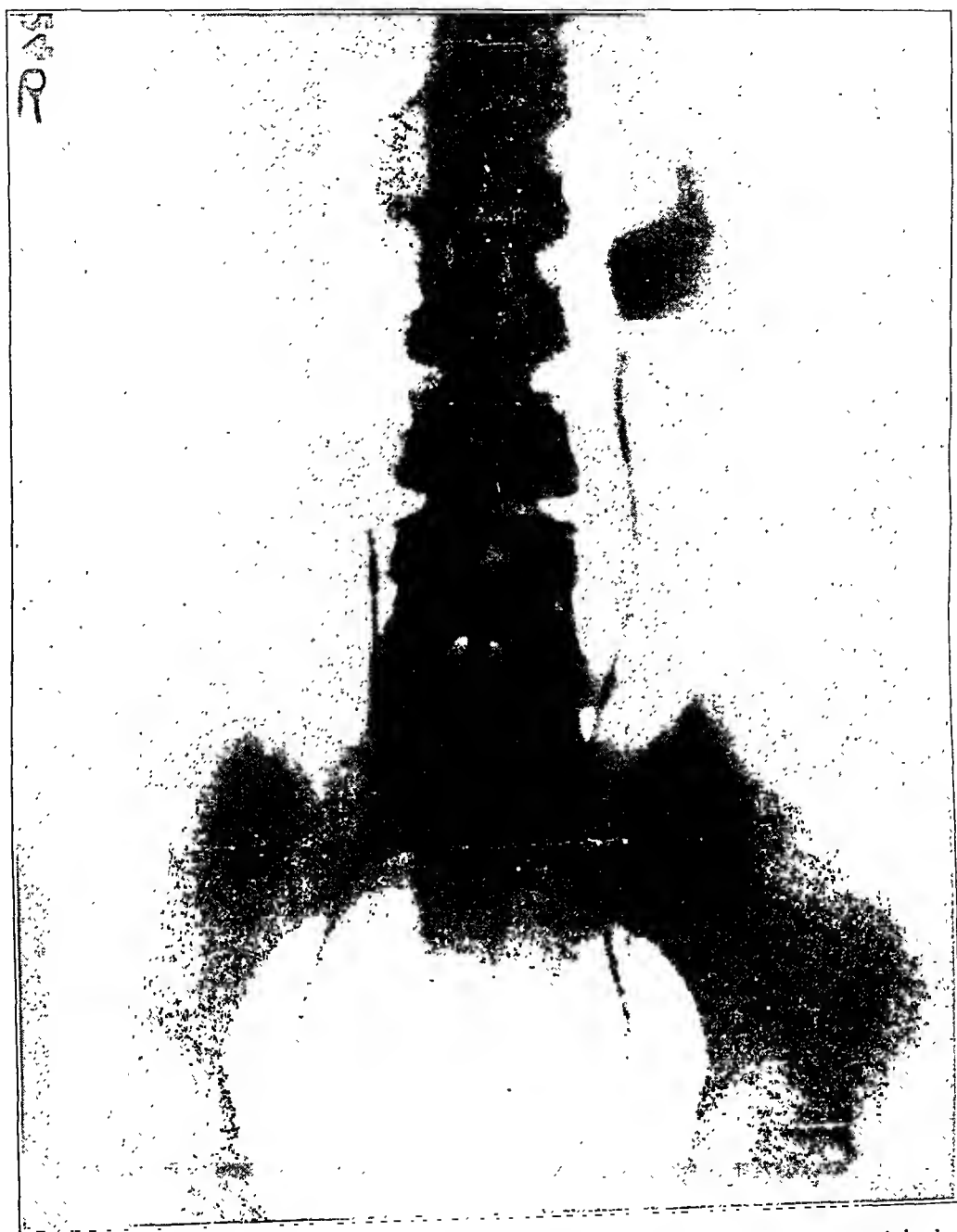


FIG. 7. Case 8. Miss J. S. Left pyeloureterogram. Stricture at ureteropelvic junction, pyelectasis. See text.

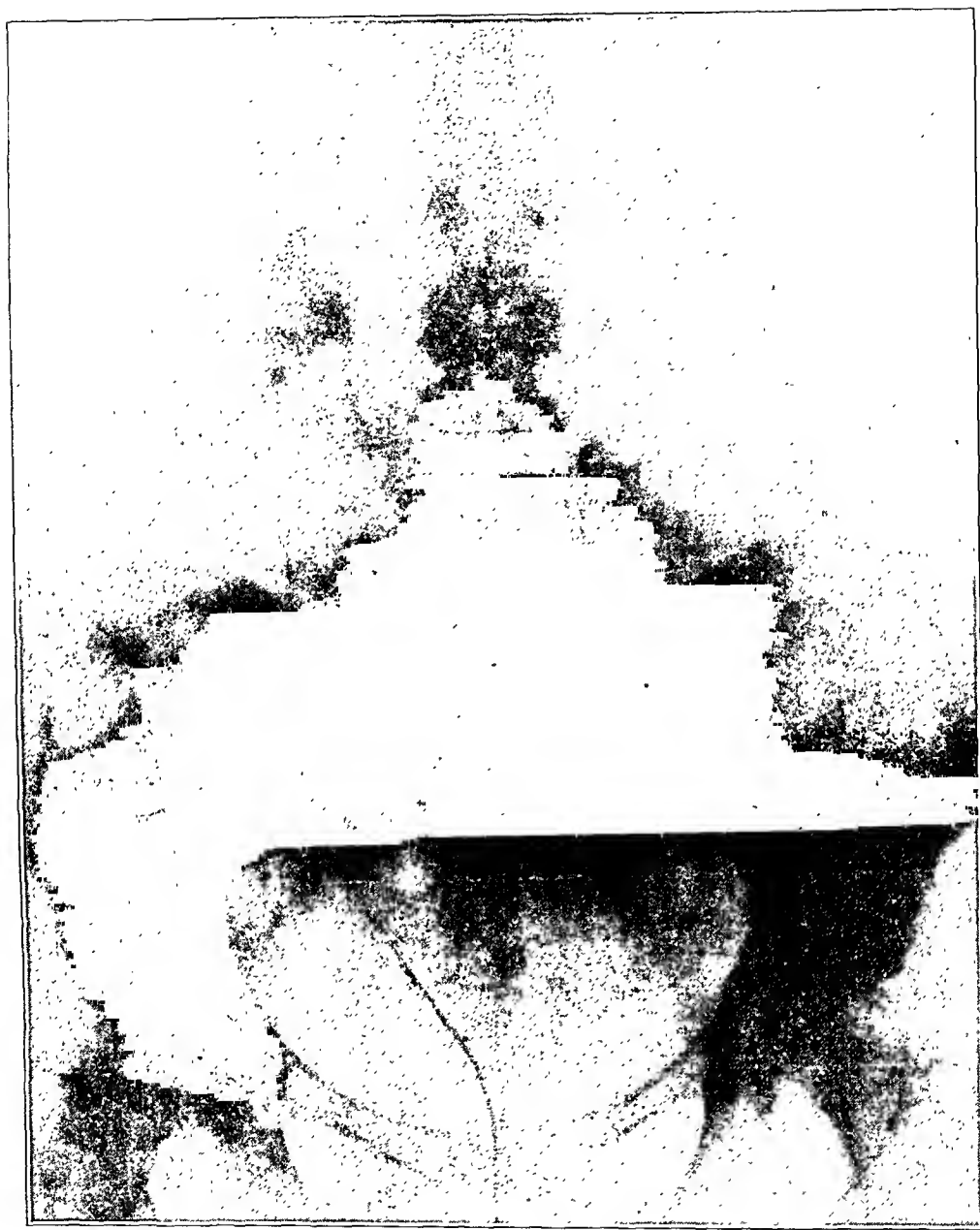


FIG. 8. Case 49. Miss W. Bilateral pyeloureterograms. Multiple strictures both ureters; more accurate demonstration made by bouginage. Also slight right hydronephrosis. This patient had a series of antecedent infectious diseases and chronic tonsillitis.



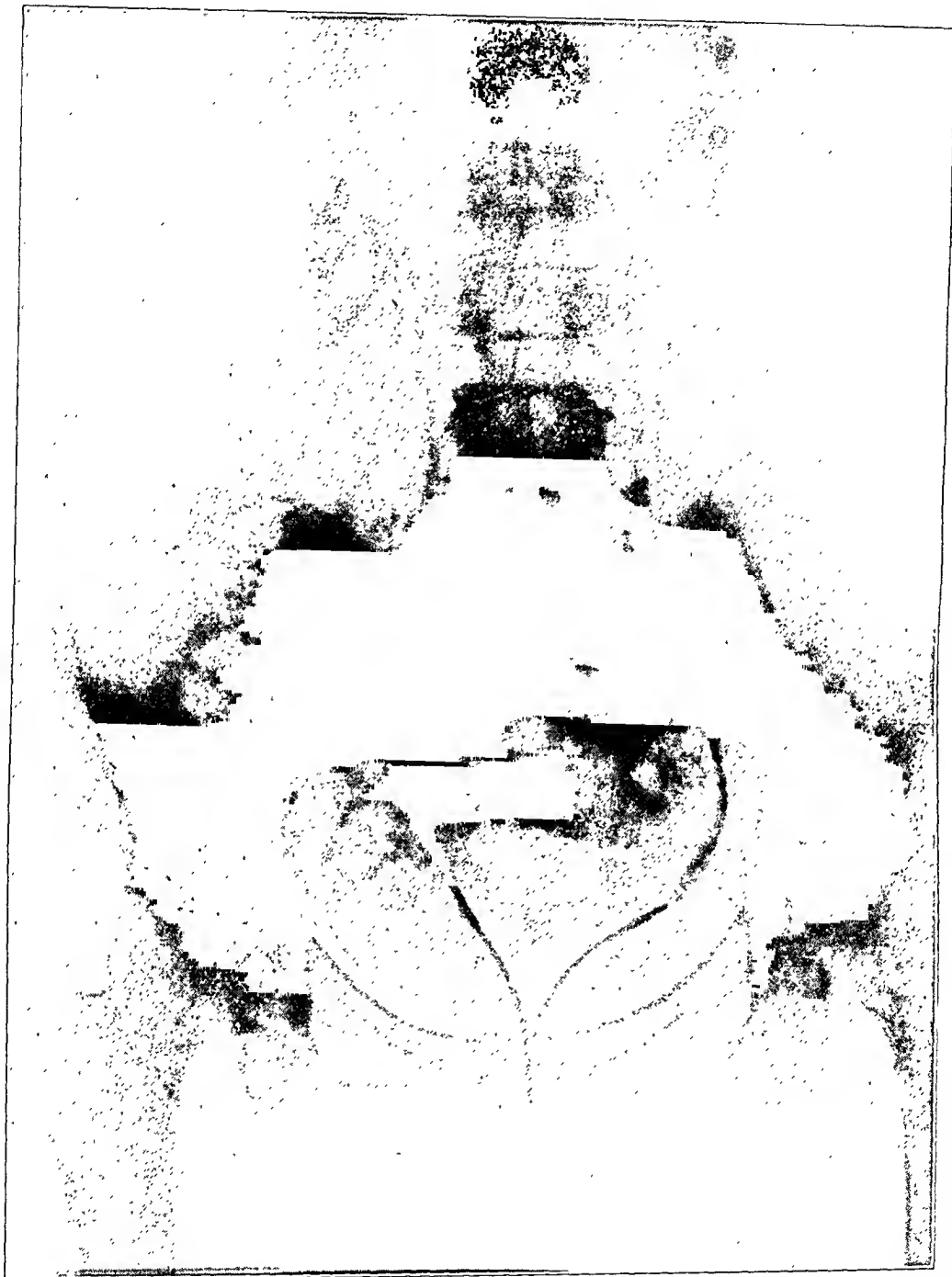


FIG. 9. Case 53. Bilateral pyeloureterograms. Multiple irregularities of ureters proven strictures by careful instrumentation.

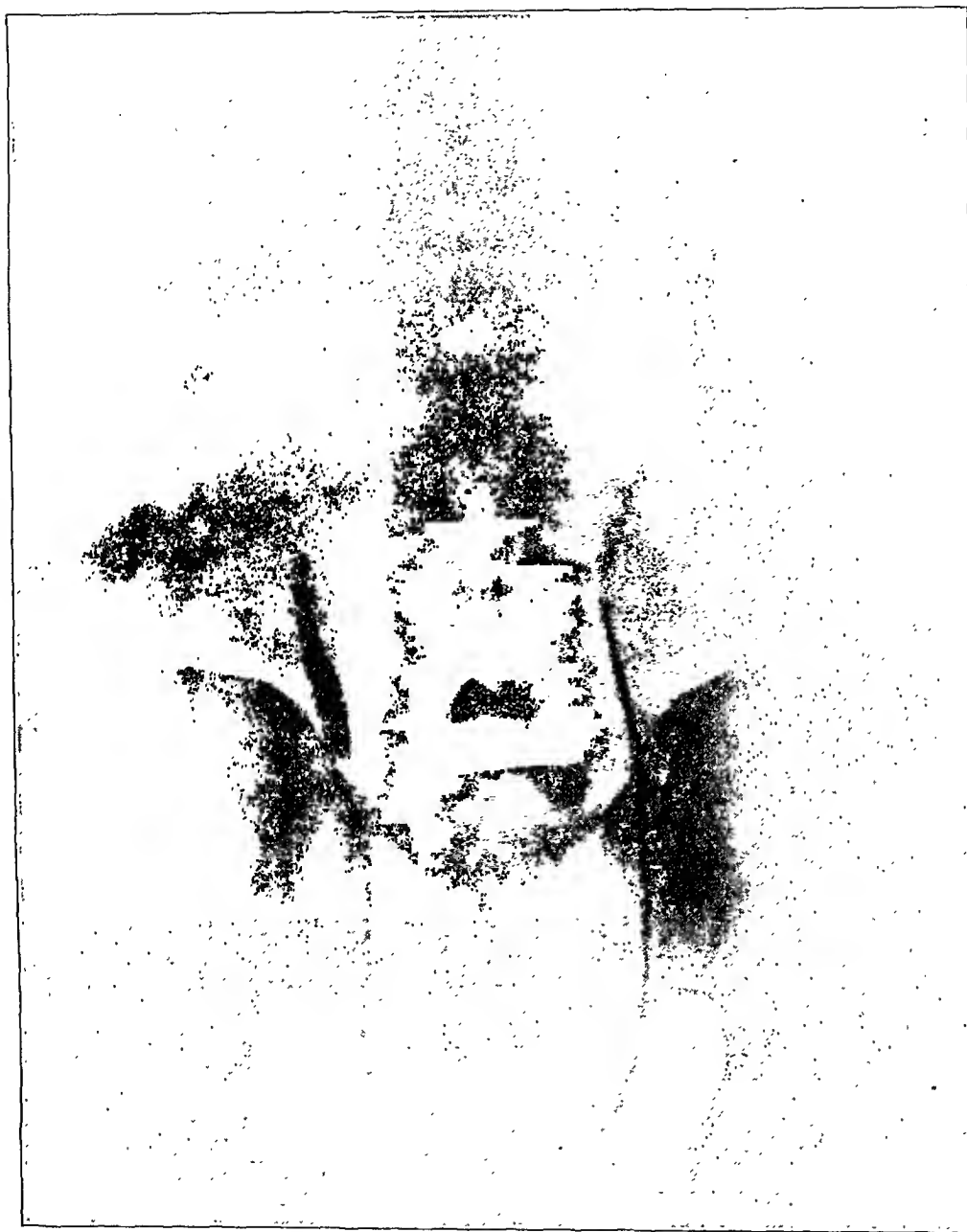


FIG. 10. Case 33. Mr. D. G. Bilateral pyeloureterograms, demonstrating strictured areas in upper ureteral segments; both associated with pyelotomy for stone. Following operation on left side kidney has atrophied and is functionless; only a small part of pelvis remains.

to such involvement. Thirty-nine cases showed unilateral stricture and 23 bilateral pathology.

### CONCLUSIONS

1. We believe that ureteral stricture is of very frequent occurrence and that it represents a definite clinical entity.
2. The recognition of symptoms suggestive of ureteral pathology does not require special training.
3. We believe that patients in whom a diagnosis of chronic appendicitis seems logical but unsupported by a history of attacks as well as patients with chronic gall bladder manifestations—with or without stone—should receive an investigation of the kidney-ureter-bladder tract before surgical procedures are instituted.
4. No patient with recurrent urinary tract symptoms should be treated symptomatically alone and surgery should not be resorted to as a diagnostic procedure until after an investigation has proved with reasonable satisfaction that the ureter is not at fault.
5. Collaboration of the medical man and urologist is of great importance to the end that more cases may be brought to light.
6. The non-surgical nature of ureteral catheterization commends it as a diagnostic procedure.

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# Management of the Goiter Patient\*

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PRESENT day observation indicates that thyroid disease is more prevalent than formerly and this is especially true of the adolescent goiter. Notwithstanding a vast amount of investigative work in the problem of thyroid disease the true cause remains more or less speculative. However, there are certain essential factors that have a definite bearing on the disease, the most outstanding of which is the one evolved by Marine and Lenhart, in which they have shown rather definitely that it is in part at least an iodine deficiency disease. The literature on thyroid disease is voluminous and much attention has been given the various phases of hyperthyroidism, particularly from the standpoint of surgical treatment. More recently attention is being focused on the prophylaxis of simple goiter. It is obvious that from an economic standpoint prophylaxis is extremely important.

Municipal and State governments have taken up a consideration of the problem from the standpoint of control. As far back as 1864 France appointed a commission for the study and relief of endemic goiter. At that time the commission reported 500,000 goitrous people and 120,000 cretins. Early in the sixteenth century Paracel-

sus emphasized the relation between endemic goiter and cretinism. Goiter as a disease has been traced back to 2,000 B.C. It was in 1825 that Parry described the goiter syndrome and Graves in 1835 gave an accurate description of exophthalmic goiter. Basedow in 1840 published a monograph on the same disease. Sir Wm. Gull in 1874 described a clinical complex which represented myxedema and associated it with thyroid deficiency. Kocher in 1883 reported myxedematous states following removal of goitrous thyroids. A little later Horsley produced experimental myxedema in monkeys. In 1891 Murray and MacKenzie administered thyroid extract to myxedematous patients and obtained clinical results. A little later these observations were confirmed by Magnus Levy. Baumann discovered in 1891 that iodine was the normal constituent of the thyroid gland and in 1901 Marine showed that iodine was necessary to normal thyroid function and if sufficient iodine is present in the system, an active hyperplasia of the gland does not occur. Thyroxin as an iodine-containing hormone of the gland was isolated by Kendall in 1915. Observa-

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tion has shown that diffuse colloid and adenomatous types of colloid goiters can be prevented by the proper administration of iodine. This fact together with the fact that goiter occurs commonly where water and soil are poor in iodine, makes iodine deficiency the probable exciting cause of adolescent goiter.

The theory has been advanced that bacterial flora in the intestinal tract prevent the utilization of available iodine. This theory has been advanced as favoring the bacterial origin of goiter. It is known that the physiological activity of thyroid extracts is in proportion to the iodine content. It is known that goitrous districts are distant from the seashore and that the water supply is very largely free from iodine. Experimentally it has been shown that polluted water produces goitrous changes in fish. McGarrison champions the bacterial infections cause contending that the colon group which are water borne are responsible; that the gastro-intestinal tract infection interferes with the normal absorption and assimilation of iodine. Systemic or focal infections may produce a reaction in the thyroid resulting in thyroid toxicity, e.g. the exophthalmic type of toxic goiter. The occurrence of adolescent goiter incident to puberty and the preponderance in the female is estimated by ratios varying from 4 to 1 to 10 to 1. This preponderance in the female is responsible for the thyroid being designated as an accessory ovary. It has been known for centuries that there is an intimate relation between the thyroid gland and menstruation, that the gland enlarges

just previous to the flow. May not the stress of modern life tend to encourage thyroid disease? May it not be true that the body economy may fail to adjust itself fully to the demands of modern life and as a result increased metabolism calls for increased iodine which results in increased gland activity; therefore an increase of thyroid disease. It has been known for a long time that thyrotoxicosis in varying degrees occurs incident to stress and worry in life.

The goiter of adolescence produces few or no symptoms and is represented by a smooth, soft, uniformly enlarged gland. The exceptional case may develop symptoms in the way of increased fatigue, irritability, nervousness, tachycardia, weight loss, sallowness and constipation. This case generally represents the one whose adenoma has been present for a period of time, who is living speedily or who possibly is the victim of faulty iodine therapy. Such a condition may rapidly develop into a true toxic goiter. It is this type of case where basal metabolic rate observations are of differential value. The adolescent goiter patient with nervous symptoms unassociated with the goiter will not maintain a basal metabolic rate above normal when placed at rest in bed for a period of time. This is in contradistinction to the true toxic goiter syndrome. The goiter of adolescence untreated more often undergoes a spontaneous cure. The exceptional case may develop cystic, colloid or adenomatous degeneration which later may result in toxic goiter or give mechanical

disturbance by pressure on adjacent structures.

Common signs of hyperthyroidism are (1) cardiovascular reactions that represent an increased minute flow of blood from the heart; (2) increased hypertension, sweating and elevation of surface temperature, increased heart rate; (3) increased caloric intake to maintain body weight; (4) a group of nervous symptoms resulting from irritation stimulation and fatigue of the nervous system resulting in visceral and tissue degeneration.

The symptoms of exophthalmic goiter are those of hyperthyroidism accentuated plus exophthalmos. The cause of exophthalmic goiter is not known. It represents a stimulation from some unknown source on the entire thyroid gland producing an agent probably abnormal in quality and in quantity, which in the tissues of the body cause all the phenomena of the disease. Exophthalmic goiter develops abruptly in contradistinction to hyperthyroidism which develops insidiously and occurs more commonly in an earlier period of life than hyperthyroidism. The basal metabolic rate in exophthalmic goiter averages much higher than in hyperthyroidism. It is interesting to note that a large per cent of exophthalmic patients have an enlarged persistent thymus. Cardiac disturbances are more marked in exophthalmic goiter than in hyperthyroidism. Auricular fibrillation is relatively common. The clinical course of exophthalmic goiter is variable. The milder case goes on to spontaneous cure but the severe case succumbs to the disease if not relieved by medical

or surgical management. It is important to operate the exophthalmic case early before irreparable damage is done to the heart musculature and other viscera. The exceptional case will respond to medical management.

There is a diversity of opinion even now as to what shall constitute the management of the goiter patient. More careful clinical study together with metabolic rate observations no longer leaves the diagnosis uncertain in a large per cent of the toxic goiter cases. Surgical treatment of toxic goiter was introduced empirically and in spite of much scientific knowledge which has been developed about the disease complex, it still remains popular as satisfactory treatment in a large per cent of the cases for the reason that no other form of treatment has so routinely given satisfactory results. Whatever more than a dysfunction of the thyroid gland characterizes the picture known as toxic goiter, the fact is established that removal of a gross portion of this dysfunctioning gland results in an interruption of the symptoms which characterize the disease. If removal of sympathetic ganglia for angina pectoris (it matters not what may be responsible for the symptoms of angina pectoris) had resulted in satisfactory clinical improvement no doubt the operation would have been popularized as goiter surgery has been popularized. Toxic goiter, whether toxic adenoma or Graves' disease is primarily a medical disease and should have primary medical management. The value of absolute bed rest plus the judicious use of iodine therapy in the form of Lugol's solution should be

taken advantage of in the routine management of every case of hyperthyroidism and bed rest must mean rest away from home environment always. It is absolutely impossible to manage satisfactorily the toxic goiter patient in the home. Such a period of management has three purposes, first to confirm a diagnosis; second to prepare for surgery if surgery is advisable and third to determine the case that will satisfactorily respond to medical management. If such management is practiced as a routine, the psychoneurotic, the neurasthenic and the nervously unstable with the irritable heart will not be subjected to needless and harmful surgery. I have been surprised myself how frequently I have found surgery not to be necessary after such a period of management where earlier observation was misleading not only diagnostically but therapeutically. If surgery is applied routinely early without careful diagnostic discrimination surgery will be abused. If preliminary management is not practiced as a routine you will have no satisfactory means of absolutely determining the border line case or ruling out the psychoneurotic with a colloid goiter. This puts goiter surgery on the same plane with the appendectomy—Deaver's dictum, "better to take out a normal appendix than to leave in a diseased one." There are those who argue that goiter surgery is not scientifically sound, that no satisfactory explanation has been made of the rationale of the procedure and therefore it is to be condemned. Until medicine has found a satisfactory cure for a much larger per cent of the cases of toxic goiter than is true today I shall

be rather liberal with the surgeon's lack of satisfactory explanation of the cure of the disease but be guided by the results that have been so satisfactory in so large a per cent of cases subjected to goiter surgery. In a recent visit to European clinics I was greatly surprised to learn that they believe in certain clinics that the treatment of goiter is largely medical. I could excuse them on the ground that they see comparatively little goiter and therefore their experiences have not gotten them into the proper channel. X-Ray and radium as a means of treating goiter have not gained popularity generally; our results have been disappointing and I am of the opinion that radium therapy has very limited value in the treatment of toxic goiter. Lugol's solution in ten, twenty or thirty drop doses t.i.d. has been helpful in lessening toxic symptoms in all cases either exophthalmic or toxic adenoma. Frequent basal metabolic rate determinations have been valuable in checking clinical improvements as well as helpful in determining diagnosis. I think results of metabolic tests should be carefully checked as there is great liability to error if technique and conditions are not carefully controlled. I do not think slight elevations in basal rates should be given weight independent of clinical signs. We hear much of the abuse of iodine administration either as contained in iodized salt or other forms of administration. I think much of this criticism is overdrawn and conclusions are gotten without facts to prove. The tremendous value of iodine administered in proper quantities as a preventive of goiter has been

accepted. Because a few isolated cases develop toxic goiter who have taken iodine or iodized salt as a preventive should not answer as an argument against the judicious use of iodine. I would rather believe that the quantity of iodine was too small to be of value in isolated cases. It will take careful observation to prove that the judicious use of iodine as a preventive is objectionable. Of course the injudicious use of iodine in any form is to be condemned. The insidious development of toxic goiter with gastro-intestinal symptoms is not always easy of diagnosis. The high basal rate in this type of case is very satisfactory confirmatory evidence. Goiter hearts lead to diagnostic confusion, this is particularly true of disturbed mechanisms such as auricular fibrillation. Control of fibrillation and re-establishment of compensation clear the confusion. Most cases of fibrillation will respond to intensive digitalis therapy and I prefer intravenous digitalis therapy. The occasional case that is not controlled with digitalis will be controlled with quinidine in 2/10 gram doses q 4 or 6 h. If fibrillation is not controlled surgical interference is advisable in spite of fibrillation. A fibrillating heart that fails to respond to therapy before surgery will often respond after surgery. The case that encourages you to apply medical management is the one that shows a definite improvement after a period of two or three weeks at rest in bed with iodine therapy, in which there is a distinct lessening of tachycardia, tremor, increase in weight and a definite drop in the basal metabolic rate. Graves' disease developing

incidental to diabetes is controlled with diabetic management where insulin therapy is taken advantage of. Mrs. G. age 58 yrs., a severe diabetic, managed in 1920-21, developed acute marked signs of Graves' disease early in 1922. She was managed with difficulty over a period of months and suffered marked weight loss. Late in 1922 insulin became available and was administered continuously in varying quantities for a period of six months during which time the symptoms of Graves' disease largely disappeared, the metabolic rate approached normal, there was a weight increase from 111 lbs. to 138 lbs., there was a marked drop in cardio-vascular hypertension which had ranged from 160/90 to 190/100, and a distinct improvement of carbohydrate tolerance. She was under observation throughout 1924-25 during which time her carbohydrate tolerance remained relatively good and the symptoms of Graves' disease had completely subsided. This recovery took place without apparent visceral damage and it would seem that insulin as an internal secretion played some part in the amelioration of the symptoms of Graves' disease.

In a series of 83 cases of thyrotoxicosis managed in the last few years, 32 were subjected to medical and surgical management and 51 to medical management alone. Eight cases of Graves' disease had bed rest, iodine therapy and high caloric feeding an average of 25 days before surgery. There were 5 males, 3 females and the average age was 41 yrs.; the average metabolic rate was plus 66 and the average metabolic rate after surgery



was plus 27. There were no deaths in our clinic and complete restoration to work was obtained in all cases. One patient, a male, age 36 yrs. showed very decided improvement under medical management but on account of his work being that of a detective it seemed advisable to have surgery rather than subject him to the possible uncertainty of final medical cure. He was apparently a good surgical risk and was operated in another clinic but for some unaccountable reason developed a severe hemorrhage and died twelve hours after surgery; but this was not a goiter death. Twenty-four cases of toxic adenomas were subjected to surgery after an average period of medical management of 3 months, 17 days. There were 5 males and 19 females, the average age was 39 yrs., the average metabolic rate before surgery was plus 57 and after surgery plus 16. Five cases of exophthalmic goiter were subjected to medical management alone—2 males and 3 females; average age 43 yrs., average metabolic rate before management was plus 21. There were seven—plus 16. These cases were kept under observation over an extended period and have been restored to full working efficiency. Forty-six cases of toxic adenoma were managed medically, 9 males and 37 females, average age 41 yrs., average basal rate before management was plus 47, after management was plus 21. There were seventeen cases classified as hypothyroid, 2 males and 15 females in which the basal metabolic rate varied from minus 5 to minus 29 with an average of minus 7, one of which was a marked

case of toxic adenoma with a maximum basal rate of plus 44 and became a hypothyroid on medical management with a basal rate of minus 29. The other was a marked exophthalmic case with a maximum basal rate of plus 45, who developed signs of myxedema with a basal rate of minus 23 two months subsequent to surgery. Three of these cases were definitely myxedematous. All responded to thyroid therapy.

It remains to be seen what the eventual outcome of the toxic goiter case will be that responds to medical management. At most medical management must be regarded as an arrest of the disease activity but not always an absolute cure. A number of these cases were managed medically for the reason that they refused to have surgery. It is gratifying to report that not a single fatality in our clinic has occurred in the last five years in the toxic goiter cases managed either medically or surgically. Team work in the goiter problem is highly important. The condition is both medical and surgical. Early surgery without medical management is just as faulty as late surgery after there has been extensive visceral damage. Post-operative management as it applies to rest, exercise, diet, cardiac complications and iodine therapy with metabolic rate checks is a part of team management. For the present we should regard surgery as the method of choice in treating the toxic goiter case. Certain cases will respond to medical management but they are a smaller per cent of the total cases. More careful preparation and discrimination should characterize

the management of the goiter patient. Not every case with a lump in the neck should have surgical interference. A diagnosis of goiter in any of its forms does not spell surgery, necessarily.

A master surgeon has said that a successful operation only marks the beginning of the treatment of Graves' disease and here the factors to be emphasized are the same as those of pre-operative management, viz. rest, mental

and physical, which cannot be satisfactorily obtained in hospital wards. A prolonged vegetative period should follow recovery, whether the management be surgical or medical. It is extremely important to have surgical treatment early where surgery is indicated. The disappointing results of surgical care of toxic goiter may be due largely to two factors, one, the delay of operation and the other, faulty medical management.

## Editorial

### *SOME SEX DIFFERENCES IN THE PATHOLOGICAL PIC- TURE OF SYPHILIS*

It has long been recognized that there are very marked differences clinically in syphilis in the two sexes, but the full import of these variations is not usually brought to the mind of the internist as constituting definite factors in diagnosis. Both sexes are usually approached along the same line diagnostically, and as a result syphilis is often not suspected in women when it does exist. Unfortunately most of the textbooks have failed to recognize these important differences at all or only very incidentally; and only three of the most recent works on syphilology make any adequate mention of them. In the examination of any given female patient for evidences of syphilitic infection it must be borne in mind that in a very large number of syphilitic women there will be no history of primary or secondary lesions given by the patient and that a very large percentage will constantly show a negative Wasserman reaction. On the whole typical chancres are comparatively rare in women owing to the structure and conformation of the genital organs, and also because many infections of the female are seminal infections. Chancre d'emblée, or hidden or concealed chancres are very much more frequent in women than in men. Pri-

mary lesions within the genital organs are relatively rarely recognized. On such tissues as the moist mucous membranes of the vulva and cervix, and possibly also in the endometrium, the primary lesion may show such appearances that it may easily be mistaken for something else, and this mistake, particularly as to suspected malignancy, not infrequently occurs. The secondary skin eruptions are more frequently overlooked in the female than in the male. In a large proportion of female syphilitics there will be elicited no history of either primary or secondary lesion. On the other hand, constitutional symptoms, such as fever, anemia, rheumatic or neuritic manifestations and various so-called "toxic" symptoms usually replace the customary history of early syphilis. The female undoubtedly has a higher degree of natural immunity or resistance to the spirochete pallida than has man. This biological difference is greatly increased during the child-bearing period, particularly if the infection is a conceptional one. The woman who has a syphilitic embryo, fetus or child is always syphilitic herself, but she may show absolutely no clinical signs of such an infection on her part. Her Wassermann may be consistently negative for many years. The only sign of her syphilis is the fact that she produces syphilitic children, or constantly aborts. Never-

theless, at the time of the menopause she usually shows a positive Wassermann or develops unmistakable clinical signs of the disease. This immunity of the woman during the child-bearing years is one of the most remarkable features of syphilis; but unless this fact is known and understood by the clinician, he is certain to go far astray in his diagnostic evaluation of many female patients. Further, if he fails to recognize this possibility, he deprives many syphilitic children of the chance of antenatal treatment. In such women treatment is of value to the fetus and usually not to them. Moreover, he should be prepared to advise or to administer active antisiphilitic treatment to such women as have borne syphilitic children as they approach the menopause when such latent syphilis tends to become active in them. Here also in the stage of renewed activity syphilis shows very great sex differences as to organs and tissues involved. Only rather rarely does the syphilitic women develop serious syphilitic lesions in aorta or heart. While colored women and occasional white women who have been engaged for a long time in hard manual labor may show as severe aortitis or myocarditis as any male, such cases are very unusual. The average female with latent syphilis has very slight lesions in aorta and heart which give her no especial clinical manifestations and play no important role in producing cardiac insufficiency. Aortic aneurism is very uncommon in women; and cardiac death from syphilis rare also. On the other hand the liver is very

frequently involved in such females with latent syphilis. As the menopause develops obscure abdominal symptoms appear; and at operation or autopsy a well-developed hepatic lobatum is found. It is remarkable to what degree a gummatous hepatitis may develop with few or no symptoms. Milder degrees of this disease are usually referred by the clinician to gall bladder disease. The pancreas and adrenals are also much more frequently seriously involved in women than in men. The pancreatic condition is usually diagnosed clinically as disease of the gastro-intestinal tract; while apparently there is no well-defined clinical picture of the adrenal localization except in the most severe cases in which an addisonian syndrome is present. Gummatous strictures of the rectum are very much more frequent in women at the menopause period, than they are in the male. The condition is almost always suspected to be malignancy; and numerous cases are operated upon with such an incorrect diagnosis, as shown by microscopical examination. The latter, however, should always be made before the operation, and not after it. Gummatous lesions are also more common in women in the pectoral regions, nose and mouth than in the male. A still more striking sex-difference exists. In the male the latent syphilitic always shows testicular lesions in the form of an orchitis fibrosa; but in the female the sex gland, the ovary, seems to be immune to the spirochete. It is very doubtful if anyone has ever seen a positive syphilitic lesion of any kind in the ovary. If such lesions exist they are either

extremely rare or we are unable to recognize them. In the latter case it remains for coming pathologists to give them recognition. There are, then, very remarkable differences in the pathological pictures of syphilis in the two sexes. Some of these differences may be explained as the result of differences in environment, habits, occupation, and general hygiene; others must depend upon deep-seated biological or endocrinal differences. The especial degree of clinical freedom from the disease

which the latent syphilitic woman possesses during the child-bearing disease must depend upon some especial protective mechanism active at this time. While we cannot explain these differences in reaction to a given infection, it is very necessary to know that they exist, and to take account of them whenever the question of syphilitic infection in woman comes up, and to recognize the fact that syphilis in women often cannot be diagnosed by the Wassermann reaction.

## Abstracts

*Effect of Ultraviolet Light on the Blood of New-Born Infants.* Erythrocytes and Hemoglobin. By H. N. SANFORD (Amer. Jour. of Dis. of Children, Jan., 1928, Vol. 35, p. 9).

With the increasing use of ultraviolet light as an important therapeutic measure for children, it is obviously necessary to ascertain the effect of this procedure on the young organism. In a previous paper the writer has shown that ultraviolet light is capable of increasing the blood platelets in the new-born. The present investigation deals with the effect on the erythrocytes and hemoglobin, and is based on observations on a series of 200 new-born infants during a period of eight months. The erythrocyte count and hemoglobin determinations were made within six hours after birth and at twenty-four hour intervals thereafter. These were made at the same time every day. Treatments with the ultraviolet ray were begun on alternate infants on the second day, and continued thereafter at the same time on each of the following four days. The method of Newcomer for the determination of the hemoglobin was used. Blood was taken from the skin of the heel after thorough cleansing with soap and water and alcohol. In the normal series the number of erythrocytes was found to compare favorably with that found by other investigators. The sex variations were within the limits of normal technical error, and not worth recording. The average count in the normal series ran from 4,500,000 to 5,800,000. Since the observers have reported extremely high hemoglobin values during the first week of life it is of interest that this series of cases showed an average much lower than is usually supposed, 94-115 per cent. Two patients in the series showed a well-marked anemia although the physical

observations were normal. As far as the literature is concerned, anemia in the new-born is considered very rare, there being only five cases reported. Sanford believes that anemia is not uncommon but is not diagnosed because a blood count is not made. Treatments with the ultraviolet ray were given by means of an air cooled mercury vapor quartz lamp, of 110 volts, 60 cycle and 10 amperes. A voltage of 70 was always administered and maintained throughout this exposure. Dorsal and ventral surfaces were exposed for one minute each, the time being increased one minute a day until the fourth day. As a result of this investigation Sanford found that the percentage of hemoglobin in the blood of new-born infants is not so high as is usually quoted. Short exposures to ultraviolet light increase the hemoglobin content and number of red cells to a slight extent in an average number of cases, with a rapid return to normal. In cases in which the hemoglobin content and number of red cells are lower than normal the increase in both hemoglobin and number of red cells is greater, but they tend to remain nearly normal. The results would indicate a stimulation of the hematopoietic organs. The increase in hemoglobin content during irradiation might be due to the decreased volume of blood resulting from loss of water from the blood during the first days of life. As there is an increase in the number of red cells in cases in which the hemoglobin is increased, however, it does not appear that there is an actual increase of the hemoglobin content in individual cells. The subject of blood volume in the new-born is not well understood and deserves more study. The few cases examined after discharge from the hospital showed normal values. They indicate that the hemoglobin content and the red cell count drop rapidly

to a normal level after irradiation. As far as the literature is concerned Aschenheim, Gelera and Barenberg found no increase in hemoglobin and red cells after ultraviolet irradiation, while Miles and Laurens did. Graffenburger, Marti, Borisson, Orum, Aschenheim, Koster and Laurens and Sovy all found a decrease in hemoglobin content and red cells in darkness and an increase in sunlight. On the other hand, Grober and Sempell examined horses kept for from five to ten years in mines, and did not find a decrease in either the hemoglobin content or the number of red cells. Likewise, Blessing, a surgeon on the Nansen expedition, found no change in hemoglobin content or the number of red cells in the members of the expedition after their exposure to the long polar night.

*Experiments with Diabetic Urine on Rabbits.*

By ALICE TWEED MARSTON. (Thesis in Bacteriology, Univ. of Penn., 1927.)

The cause of diabetes has attracted little attention, either clinically or experimentally. Certain experiments by D. H. Bergey at the University of Pennsylvania seemed to point to a filtrable virus as the direct causative agent. His conclusions were so revolutionary that further study and experiment along the same lines seemed desirable. Numerous investigators have thought that diabetes is possibly contagious, basing this belief on the fact that the disease often occurs in husband and wife, nurse and patient, and children in the same family. However, such coincidences may be explained on other grounds, familial susceptibility, faulty hygienic habits or pure chance. The present investigation concerned itself with the intravenous injection of diabetic urine filtered through diatomaceous earth filters, or by the introduction of unfiltered diabetic urine by stomach tube. Rabbits were used for the experiments. The negative results obtained would indicate that glycosuria cannot be produced in rabbits by intravenous injections of filtered diabetic urine. Some of the experiments as to the glucose tolerance tests showed, however, that the blood sugar

in injected animals rose above normal and returned to normal more slowly than in the case of uninjected animals, thus suggesting some change in the condition of the injected rabbits. Nothing in this investigation can be taken as supporting any definite statement as to the infectious nature of diabetes mellitus.

*Myxedema Heart.* By GEORGE FAHR (Amer. Heart Journal, October, 1927, p. 14).

Fahr believes that if dilatation of the heart, dyspnea on exertion, anasarca of the dependent portions of the body, passive congestion of the liver, and edema of the lungs are symptoms of heart failure, then heart failure of greater or less degree is not very infrequent in myxedema. If the complete or nearly complete relief of these symptoms by medication with thyroid extract in amount sufficient to bring the basal metabolism up to normal and to cause the myxedema to disappear is evidence that both the myxedema and the heart failure have the same cause, namely, thyroid deficiency, then the term myxedema heart is justified. He reported, in 1925, two cases of heart failure of this type, apparently cured by thyroid medication. Previously Zondek had reported six cases of heart failure to thyroid deficiency which were cured by thyroid medication. Assman, Meissner, and Curschman have reported in the German literature similar cases; Lambry, Mussio-Fournier and Waker one case in the French literature; and Means, White and Krantz one case in this country. On the other hand Willius and Haines, in a study of 162 cases of high grade myxedema, found no case of "heart failure or of organic cardiovascular disease that could be justly attributed to the myxedema. There were numerous electrocardiographic abnormalities which disappeared under thyroid medication. The data presented do not justify the establishment of a cardiac syndrome characteristic of myxedema." Willius and Haines' conclusions are very hard to understand. With the largest material of myxedema cases in the world they have been unable to find a single case of car-

diac failure attribute to myxedema, whereas in other clinics where the amount of material is very much smaller numerous cases of heart failure unquestionably due to the same factors as the myxedema have been found. In the past four years Fahr has seen six such cases at the General Hospital and the University Hospital in Minneapolis. All six cases showed more or less heart failure, the symptoms and signs of which receded partially or completely on thyroid medication. These six cases are reported in this paper. Fahr concludes from this study that heart failure not very infrequently accompanies myxedema and disappears with the myxedema on treatment with thyroid extract. This heart failure is characteristic of myxedema as only thyroid extract will completely alleviate it. It therefore deserves the name of myxedema heart, the term applied by Zondek to this condition in 1918. As he was the first physician to point out the outstanding features of cardiac failure in myxedema, the name applied by him should stand despite the fact that it might be improved upon.

*Innervation and Tumor Growth.* A Preliminary Report. By HORST OERTEL (Canad. Med. Jour., 1928, XVIII, p. 135).

It is generally stated in the leading textbooks on pathology that neoplasms have no nerve-supply of their own, and this statement has been emphasized as one of the most important proofs of the autonomous and emancipated nature of tumor growth. What nerve structures have been demonstrated histologically in neoplasms have been regarded as remains of the original nerve-supply of the part. The older students of this question invariably reported negative results. That such developmental disturbances as nevi may contain nerve fibers has nothing to do with this question, inasmuch as they do not represent true autonomous blastomas, although such may arise in them.

The question has been re-opened by the work on experimental tar-cancer. Itchikawa claims to have found nerves in tar-cancer and in a spontaneous cancer of the horse. Nakamoto, on the other hand, finds no nerves in tar-cancers. Oertel, using a modification of Bielschowsky's nerve-stain, believes that he has been able to demonstrate a nerve-supply in several types of cancers and sarcomas of man. By this method nerve fibers are stained black; other fibers and reticulum, pale brown or yellowish. The nerve fibers are also characterized, in addition to their staining by their manner of distribution, method of branching, and manner of approach to the cells. Six illustrations are given: Squamous-celled cancer of the cervix, cancer of prostate, metastatic in pelvic lymph node, primary adenocarcinoma of lung and adenocarcinoma of rectum metastatic in the kidney. There is no detailed description of the fibers shown in these illustrations, and no control proofs with other nerve stains are offered. The text of the article is argumentative rather than demonstrative. It cannot be said that the illustrations are in themselves convincing that the fibrils present are anything other than reticulum or elastic tissue fibrils. As far as any special staining differentiation is concerned between nerve and reticular fibrils there does not appear to be such in the photomicrographs. Should some of these fibrils actually be nerve fibrils it still remains to be proved that they are not the remains of the original nerve supply of the tissue. The resistance of nerve trunks and fibers to neoplastic invasion is well known; they may remain apparently unaffected when all other normal structures have disappeared before the invading tumor cells. Further, if nerve fibrils should be demonstrated in the walls of the vessels of neoplasms, it does not necessarily follow that these fibers have any relation to the parenchymatous cells of the neoplasm.



## Reviews

*Treatment of Disease in Infants and Children.* By HANS KLEINSCHMIDT, M.D., Professor of Pediatrics, University of Hamburg. Authorized Translation of the Fifth German Edition with Additions. By Harry M. Greenwald, M.D., Attending Pediatrician to the United Israel Zion Hosp.; Consulting Physician to the Hebrew Infant Home of Brooklyn, Brooklyn, N. Y. 359 pages. P. Blakiston's Son and Company, Philadelphia, 1928. Price in cloth, \$5.00.

This book had its origin in Czerny's clinic in Berlin, and was originally intended for a small group. It was, however, very favorably received in Germany, and has had five editions since 1918. It has also been translated into the Russian and Portuguese languages. In it the author has endeavored to collect only those therapeutic measures in the field of pediatrics which are strongly indicated and which really appear necessary for successful treatment. He has wished to avoid polypragmatism, however, and has, therefore, omitted a great number of therapeutic procedures and drugs the addition of which might have encouraged the latter. Kleinschmidt believes that dietic and physical methods are of first importance in the treatment of diseases of children and that medicinal treatment is only of secondary importance. In the last few decades great strides have been made in the field of dietetics, and this subject is, therefore, discussed at greater length. The dosage of each drug should depend on the individual patient; the maximum and minimum doses, according to age, are given to facilitate administration. Although volumes have been written on the symptomatology and diagnosis of the diseases of children and infants, there are very few, if any, textbooks which deal purely with treatment. Usually at the

end of the description of each disease one finds only a paragraph or two on treatment, a few methods or drugs are merely mentioned, and the reader is left to himself as to which one to employ and how to proceed. This book offers the practical help of an author with a broad experience. The chapter on Nutritional Disturbances, particularly, differs from the usual book on infant feeding, in that the author describes exactly the steps the practitioner should take in the management of the disturbance in question. Generalities are omitted, and minute and specific instructions are given in each case. The translation is based on the fifth German edition with supplementary notes furnished by Professor Kleinschmidt. The translator has made a number of additions dealing with the later developments in the field of therapeutics in this country, including only these drugs and procedures which have given results in his own experience. The first six chapters deal with General Therapy, Feeding of the Normal Infant, Feeding of the Constitutionally Abnormal Infant, Nutritional Disturbances ex Alimentatione, Nutritional Disturbances not due to Alimentation, and the Care and Feeding of Asthenic Infants. There follows then a chapter on the Diseases of the Newborn, after which fifteen chapters are given to the diseases of various organs and tissues. There is a chapter on Congenital Syphilis, and the last two chapters give formulas and recipes for the normal infant and the sick infant and child. The material in this book is excellent and thoroughly up to date. It is concise, clearly stated and well-arranged. The translation is good, and the translator's notes of value. It is a valuable compendium for the practitioner, and particularly should the young physician just starting into practice find it of great service.

*Asthma, Its Diagnosis and Treatment.* By WILLIAM S. THOMAS, M.D., Associate Attending Physician in Immunology, St. Luke's Hospital, New York. 279 pages, 20 illustrations in black and white, 6 in color. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, \$7.50.

A large amount of literature dealing with the subject of Asthma has appeared in medical literature during the last five years, but as yet no book by an American author dealing exclusively with the diagnosis and treatment of this syndrome has appeared. Perhaps one reason for this is that conceptions of allergy and its manifestations are undergoing frequent changes. New data appear from time to time and give promises of improvement in methods of treatment only to be discarded afterward when their shortcomings have been demonstrated by still more recently discovered facts. Particularly does it appear that efforts toward non-specific desensitization have failed to produce the good results that were at first claimed in their favor. Authorities are at variance with each other in respect to the fundamental ideas of the nature of allergy. Nevertheless, through the maze of conflicting theories there shines an encouraging light. Improved results from the treatment of asthma have been made possible by means of the diagnostic aid of specific skin reactions to proteins and to vaccines. The intelligent interpretation of these dermal phenomena has made it possible for asthma patients to obtain material and permanent relief, whereas a few years ago the best that could be hoped for was temporary palliation of their sufferings. The author designed his book to be a practical guide to the management of asthma patients, and he has stated the theories regarding allergy in order to elucidate present-day methods of treatment. Confusion in terminology characterizes the current literature concerning the nature of asthma, and he has endeavored by using simple language to lessen this confusion. His first chapter is concerned with the definition and use of the term "asthma", a condition no longer looked upon

as a disease but as a syndrome or symptom complex, related in a manner that is only partially understood to anaphylaxis, hypersensitiveness and immunological processes. For the sake of accuracy, the term should be applied to one condition only, namely, that associated with bronchospasm, the modifying adjective "bronchial" being superfluous should be dropped. Dyspnea due to cardiac insufficiency is not asthma, nor is the designation applicable to difficulty of breathing caused by secretions in the bronchial passages or by the pressure of tumors upon them. Asthma, then, is a syndrome occurring in constitutionally predisposed people, and having as its exciting cause exposure to or contact with some substance or physical condition to which they are abnormally sensitive. It is characterized by little understood cellular and humoral changes and exaggerated respiratory reactions. Chapters II and III are concerned with the nature and causes of asthma and the pathology of this condition respectively. The methods of approach to the treatment of a case of asthma, case-history taking, physical examination, etc., are discussed in the following chapters. Protein skin tests, their technique, protein skin reactions and their interpretation, details of testing and treatment, airborne proteins, food proteins, desensitization, autogenous vaccines and skin tests, pollen asthma, its diagnosis and treatment, the complications of asthma, the non-specific radical methods of treatment, and causes of failure of treatment constitute the subject matter of the remaining chapters. A very full bibliography, complete up to November, 1927, follows. The book is well printed and illustrated. It offers an up-to-date discussion of the important subject of asthma, and its perusal will be of service to every practitioner of medicine who comes into contact with this syndrome.

*Early Medicine in Maryland.* By THOMAS S. CULLEN. Address of the President of the Medical and Chirurgical Faculty of Maryland, 1927. 15 pages.

This is a reprint of the President's Address at the Annual Meeting of the Medical

and Chirurgical Faculty of Maryland, the State Medical Society, which was granted its charter in 1799. The address sketches the history of the medical profession in Maryland, from the visit of "Walter Russell, Gentleman, Doctor of Physicke" who accompanied John Smith in 1608, up to 1927. Among the items of special interest is that in 1637 there was held an inquest on a man killed by a tree, probably the earliest recorded autopsy in America. The chief sources of authority for the history of medical science and practice in Maryland are the "Medical Annals of Baltimore from 1608 to 1880" by Thomas Quinan, which was published in 1884, and Cordell's "Medical Annals of Maryland" published in 1903. From these two works much of historical interest concerning the achievements of Baltimore physicians may be gathered; and the list given on page 3 of the "first" medical and surgical deeds accomplished by them is a long and notable one. The accounts of the early epidemics of yellow fever in Cordell's work are most interesting. The Medical and Chirurgical Faculty of Maryland is, at least, accomplishing one great deed of usefulness in perpetuating the records of the medical history of Maryland and Baltimore. In this respect it sets an example to other State Societies.

*Aluminum Compounds in Foods.* Including a Digest of the Report of the Referee

Board of Scientific Experts on the Influence of Aluminum Compounds on the Nutrition and Health of Man. By E. E. SMITH, Ph.D., M.D., Fellow and Former President, New York Academy of Sciences; Fellow of the New York Academy of Medicine, etc. 378 pages. Paul B. Hoeber, Inc., New York, 1927. Price in cloth, \$7.00 net.

The recent litigations, not yet ended, concerning the use of alum in baking powders and the alleged harmfulness of such, gave rise to many experimental researches regarding the toxicity of aluminum. These studies are widely scattered in the literature. The author believes that the subject has become of such general interest as to demand its presentation within the pages of a single volume. It will be of value not only to those interested in the particular subject, but as well to a much larger number interested in scientific methods of investigating the composition and value of food. The volume contains researches by the author which have not appeared elsewhere, and gives details of unpublished work by other investigators, including a comprehensive résumé of the investigations by the Referee Board of the United States Government. It is stated to be a complete, authoritative and impartial survey of this disputed question, and as such is valuable to physicians, chemists and all others interested in this subject. A valuable bibliography is included.

# College News Notes

## *TWELFTH ANNUAL CLINICAL SESSION, NEW ORLEANS, MARCH 5-9, 1928*

The Twelfth Annual Session has passed into the history of the College. There can be no doubt, judging by the almost universal comment, that as far as the General Sessions were concerned this was the most successful meeting the College has yet carried out. Many of the addresses were concerned with clinical and experimental material of the highest order, even epoch-making in certain instances. The others represented important reviews and résumés of clinical questions of prime importance, and from every one of them some important fact or viewpoint could be obtained. An unusual degree of interest was shown by the large attendance at each session; even the last one had a well-filled auditorium. There were nearly one thousand registrations. The official meetings were well attended, and much business of great importance to the College was carried out, marking important advances in policy. A very large list of new Fellows and Associates passed a more critical survey of their qualifications than ever before, and the College may congratulate itself upon the high quality of the newly-elected, including some of the leading internists of the country. The names of these will appear in the April number, together with those of the new officers and committees. The publication of the addresses and papers will begin in the April number of the Annals; and it is hoped that this meeting will be recorded in full in the journal. New Orleans more than made good as a most interesting city. The historical interest of the old French quarter added much to the pleasure and charm of this—the first Southern meeting of the College.

## *OBITUARIES*

Dr. Richard Bew, Atlantic City, New Jersey—September 4, 1927. Killed by propeller of a yacht while swimming. Elected a Fellow of The College December, 1926.

Dr. Bew, who was born in Germantown, Pa., in 1882, is survived by his wife, who was Elsie Gould, daughter of Mrs. T. K. Roberts, of Atlantic City, and two sons, Richard, Jr., 21, a life guard here and in his third year at Lafayette College, and Walter, six years old. He came to Atlantic City in 1922 to practice. He saw medical service during the World War. He was a Republican in politics and an Episcopalian.

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Dr. Charles Giffen Beall, Fort Wayne, Ind. (Fellow, November 3, 1922). Died February 7, of Pneumonia following a cerebral hemorrhage; aged 46.

Dr. Beall received his medical degree from the Fort Wayne College of Medicine in 1904 and afterwards did postgraduate work at Allgemeines Krankenhaus, Munich. During the World War, he served as Captain of the Medical Corps, United States Army. Since 1923, Dr. Beall has been Chief of the Medical Service at Fort Wayne Lutheran Hospital, and at the time of his death was on the staffs of the Indiana School for Feeble-minded Youth, and the Irene Byron Sanatorium of Tuberculosis.

He was a member of the Association for the Study of Internal Secretions, the American Society for the Control of Cancer, the American Medical Association, the Indiana State Medical Society, Fort Wayne Medical Society and a member of the Board of Governors of The American College of Physicians.

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Dr. Ben Carlos Frazier, Louisville, Ky. (Associate, April 15, 1920). Died February

to from an Intestinal Obstruction following Prostatic Operation; aged 63.

Dr. Frazier received his medical degree from the University of Louisville School of Medicine in 1894. He established certified milk in Louisville and other communities as officer in National Medical Milk Commission.

He was on the staff of the Childrens' Free Hospital, the University of Louisville Medical School and City Hospital, Hazelwood County Hospital for Tuberculosis, the Christian Widows and Orphans Home and the Kentucky Institution for the Blind.

He was a member of the American Medical Association, the Jefferson County Medical Society, the Medico-Chirurgical Society of Louisville, the Obstetrical Society of Louisville, the Jefferson County Milk Commission and an Associate of The American College of Physicians.

#### BUDAPEST CONGRESS PROGRESS REPORT

FEBRUARY 25, 1928.

The Vth International Medical Congress for Industrial Accidents and Occupational Diseases is definitely announced to be held in Budapest, Hungary, Sept. 2-8, 1928. National committees have been formed in the principal countries.

Since the first American announcement of Dec. 1st, 1927, Dr. Fred H. Albee, New York City, and Dr. Emery R. Hayhurst, Ohio State University, Columbus, both members of the Permanent International Committee, have been appointed Joint Chairmen of the National Committee for the United States, and have appointed Dr. Richard Ko-

vacs, New York City, as Secretary, and the others named in the letter-head to serve as members.

The Travel Study Club of American Physicians, of which Dr. Albee is President and Dr. Kovacs, Secretary, has rearranged its summer trip for 1928 especially to focus upon the Budapest Congress. Those who have already indicated their intention of attending the Congress and others are invited to join the Travel Study Club either for the entire trip or at any point. The itinerary thus far arranged calls for sailing from New York on the S. S. "München" of the North German Lloyd, on Aug. 16th: three days in Berlin, two days in Carlsbad, five days in Budapest, two days in Vienna, two days in Bad Reichenhall and Salzburg, and two days in Munich; then via Milan to Nice for two days and from Sept. 17th to 27th in Spain; sailing from Gibraltar on Sept. 28th on the S. S. "Conte Grande" of the Italian Mediterranean Service, due back in New York on October 5th. (See descriptive circular enclosed).

Correspondence regarding the trip should be had with Dr. Richard Kovacs, 223 E. 68th St., New York City.

The Annual Meeting of the Association of American Physicians will be held at the Mayflower Hotel, Washington, D. C., May 1, 2 and 3.

The American Congress on Internal Medicine and Surgery will be held in Washington, D. C., May 1 and 2. Headquarters will be at the Mayflower Hotel.

The American Association for the Study of Cancer will be held in Washington, D. C., April 30, at the Hotel Raleigh.

# Experimental Study of Acquired Resistance of the Rabbit's Renal Epithelium to Uranyl Nitrate

By WARREN C. HUNTER, M.A. M.D., *Portland, Oregon*\*†

THE ability of renal cells to regenerate after injury is scarcely mentioned in most textbooks of medicine. That these cells must have a remarkable regenerative power is best seen in the kidneys of individuals recovering from scarlet fever in which later examination will often reveal no evidence of previous damage, indicating complete restitution of damaged epithelium. The same thing occurs in the varying degrees of nephrosis accompanying many acute infections. It is also true that some cellular regeneration takes place after injury by metallic salts or other chemicals which act on the kidney.

A question which has received even less attention than regeneration is the intrinsic nature of the new epithelial cells. Are these in all respects identical with the original epithelium of the same location? Is it possible that new cells, perhaps formed while the injury is still going on, develop a tolerance, increased resistance or even a specific immunity for the substance capable of killing the original epithelium? We are accustomed to think of immunity as a general protective mechanism on the part of the body against subsequent injury by the same agent rather than a reaction of specific cells, yet in re-

cent years there has been an increasing tendency to regard immunity as a local cellular phenomenon. French investigators, particularly Besredka, (1)

(1) Besredka, Alexandre. *Local Immunization*. Williams and Wilkins Co., Baltimore, 1927.

have been especially active in this respect, while in this country the work of Rivers and Tillett, (2) Bowen (3) Mallory and Marble (4) and Gay (5) are worthy of mention.

(2) Rivers, T.M. and Tillett, W.S., *Local passive immunity in skin of rabbits to infection with (1) a filterable virus and (2) hemolytic streptococci*. *J. Exper. Med.* 41: p. 185-194, 1925.

(3) Bowen, J. A., *Production of local immunity by means of diphtheria toxin*. *J. Infect. Diseases* 36: p. 501-507, 1925.

(4) Mallory, T. B. and Marble, A., *Local immunization of rabbits to cutaneous infection with staphylococcus aureus*, *J. Exper. Med.* 42: p. 465-472, 1925.

(5) Gay, F. P. *Local or tissue immunity*. *Arch. Path. and Lab. Med.* 1: p. 590-604, 1926.

As dealing with what is probably a somewhat similar local immunity re-

\*Fellow in Medicine, National Research Council.

†From the Pathological Laboratory, University of Michigan, Ann Arbor.

action may be mentioned the recent work of Weller (6) who has been able

- (6) Weller, C. V., Tolerance in respect to the meningocerebral manifestations of acute and subacute lead poisoning. *Arch. Int. Med.* 39: p. 45-59, 1927.

to demonstrate in guinea pigs a tolerance to the meningocerebral manifestations of lead poisoning.

The question of immunity of renal epithelium is of the greatest importance in relation to our conception of tubular nephritis. In this connection Aschoff (7) states: "According to Metchnikoff, Adami and others, an essential charac-

- (7) Aschoff, L., *Lectures on Pathology*, chap. xiv, p. 340-358, Paul Hoeber, New York, 1924.

(1.) See also Gay, Frederick P., Local resistance and local immunity to bacteria. *Physiol Rev.* 4: p. 191, 1924.

teristic of the inflammatory process consists in the fact that it essentially represents a defense mechanism. In the case of infections, this defense mechanism is, as a rule, associated with a process of immunization. If a tissue or a cell develops an increased resistance against a bacterial or other poison, it is safe to assume that these particular cells have taken part in the process of defense. I am therefore prepared to express the belief that parenchymatous or tubular nephritis represents a reaction of the kidney to some poison, and that in the case of this reaction the epithelium itself takes part in the chemical transformation of the poison and in its detoxication. The kidneys of an animal which has survived a parenchymatous, i. e., a tubular, nephritis, produced by a poison, must show an increased resistance of the epithelium to further administrations of the same poison" (p. 355).

The one previous experimental investigation concerned with immunization of renal epithelium is that of Gil y Gil (8) but before discussing this

- (8) Gil y Gil, Carlos., *Die Immunität im Nierenepithelgewebe*, Beiträge zur path. Anat., 72: p. 621-653, 1924.

work it is necessary to review briefly the literature on experimental chronic nephritis.

#### REVIEW OF LITERATURE.

The literature on experimental nephritis produced by various mechanical injuries and many nephrotoxic substances, particularly the salts of heavy metals and numerous organic toxins and poisons is voluminous. Most investigators have been concerned almost entirely with the nature of the pathological lesion or functional alterations, and few have noted or given more than passing mention to regeneration of epithelium. Fewer still have concerned themselves with the problem of immunity.

With uranium nitrate most workers have limited their field to functional studies, using rather large doses and producing such extensive kidney damage that the animals died before any or but very little regeneration was possible. Such investigations, although valuable for the purpose intended, offer little of value to the present study.

Chittenden and Lambert (9) were the first to demonstrate the nephro-

- (9) Chittenden, R. H. and Lambert, A., *Untersuchungen über die physiologische Wirkung der Uransalze*. *Ztschr. f. Biologie*, 25: p. 512, 1889.

toxic action of uranium salts. Although their problem was physiological and no mention of tolerance is made

the results obtained in one dog suggest this possibility since after a period during which no uranium was given nearly ten times the original dose was required to produce the same evidences of intoxication.

At one time uranium was used by some physicians in the treatment of diabetes mellitus and several reports in which tolerance is mentioned or suggested have been found. West (10) found that larger doses were necessary

(10) West, Samuel, Brit. M. J. 2: p. 467-472, 1895. Uranium nitrate in diabetes mellitus.

to obtain the same effect in patients in whom the drug had been stopped for a time, perhaps indicating that some degree of tolerance had been acquired. Burton (11) increased the daily dos-

(11) Burton, A., A case of diabetes treated by uranium nitrate, Brit. M. J. 2: p. 847, 1896.

age of uranium from 3 to 15 grains and noted that when this amount was discontinued he could later start with the quantity last given. Duncan (12) was likewise able to increase the dosage in diabetics. Bond (13) gave a

(12) Duncan, E., Uranium nitrate in diabetes, Brit. M. J. 2: p. 1044, 1897.

(13) Bond, C. H., Uranium nitrate: its value in the control of glycosuria, Practitioner, p. 257, 1898.

diabetic patient as much as 90 grains of uranium nitrate daily for a year without harmful effect. Tylecote (14) treated a diabetic whom he believed

(14) Tylecote, F. E., The pharmacology and therapeutics of uranium. Medical Chronicle, 40: p. 379, 1904.

demonstrated tolerance for uranium. The initial dose of 3 grains daily was

increased gradually to 5 grains but discontinued because of constipation and a temporary cloud of albumin. He later began at the full previous amount without ill effect. The only recent report of this nature is that of Wilcox (15) who states that he has used

(15) Wilcox, R. W., Therapeutics of uranium nitrate, Medical Record, 92: p. 361, 1917.

uranium in some diabetic patients for months or even years without deleterious effect.

As to the lower vertebrates but one reference of tolerance to uranium has been encountered. Denis (16) gave the dog fish (*Mustelis canis*) as

(16) Denis, W. Note on the tolerance shown by elasmobranch fish toward certain nephrotoxic agents. J. Biol. Chem. 16: p. 395, 1913-1914.

much as 80 milligrams per kilogram body weight without ill effects being shown. Reference to her chart, however, shows that when 106 or more milligrams per kilo was administered the fish died within 1 to 3 days. The doses were neither repeated nor increased and for this reason it appears to the writer that tolerance was not established, at least not in the sense commonly understood.

A number of investigators have succeeded in obtaining more or less chronic renal lesions with uranium nitrate. Siegel (17) is apparently the

(17) Siegel, W., Ein Stoffwechselversuch bei Urannephritis am Hunde. Ztschr. f. exper. Path. u. Therap. 4: p. 561-575, 1907.

first. In a dog given two small doses of uranium nitrate and killed after thirty days the pathological changes in



the kidney are described as chronic parenchymatous nephritis with interstitial changes. There is no mention of regeneration.

Two years later Dickson (18) made an extensive study of uranium ne-

- (18) Dickson, E. C., A report on the experimental production of chronic nephritis in animals by the use of uranium nitrate. *Arch. Int. Med.* 3: p. 375-410, 1909.

phritis, producing in guinea pigs lesions closely resembling those seen in subacute and chronic diffuse nephritis in man. A series of subacute attacks were followed by extensive fibrosis of the kidney, in some instances proceeding to the stage of granular atrophy. He did not increase the dosage of uranium nor does he describe cellular regeneration. A second report by Dickson (19) appeared in 1912. In

- (19) Dickson, E. C., A further report on the production of experimental chronic nephritis by the administration of uranium nitrate. *Arch. Int. Med.* 9: p. 557-591, 1912.

this study guinea pigs, rabbits and dogs were employed in the hope of confirming previous observations and producing the condition among animals of different kinds which would be better suited for secondary experiments. In all animals characteristic and very similar lesions were found. A granular atrophy in which the histological picture was that of an extreme and progressive fibrosis with accompanying changes in the tubules and glomeruli he felt could not be described other than as a true chronic diffuse nephritis. In some rabbits and dogs the initial dose was increased as much as five times without killing the animals but

even the largest doses were still within the limit of tolerance for normal animals. In one rabbit Dickson saw "evidence of epithelial regeneration in many tubules."

In rabbits poisoned with uranium nitrate and potassium bichromate Smith (20) saw only patchy round cell infiltration and small areas of fibrosis

- (20) Christian, H. A., Smith, R. M. and Walker, I. C., Experimental cardio-renal disease. Study V. Smith, R. M., Experimental chronic nephritis, *Arch. Int. Med.*, 8: p. 482, 1911.

in the cortex. In the few instances where the doses were increased this was not progressive. Epithelial regeneration or increased resistance of the animals to the poisons is not mentioned.

Suzuki (21) in the course of an exhaustive experimental investigation

- (21) Suzuki, Tatzuo., *Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen*, Fischer, Jena, 1912.

of renal secretion induced varying degrees of chronic nephritis in guinea pigs by the use of uranium nitrate. In some animals receiving more than one injection the later doses were somewhat larger than at the start. In summary Suzuki calls attention to the fact that the sensitivity of the regenerated epithelium in the presence of repeated uranium poisoning becomes remarkably slight. When death of the animals occurred soon after the last administration of uranium very little injury of the epithelium in the distal and transitional segments of the proximal convoluted tubules (the selective site of injury by uranium) could be made out. Thus Suzuki, although giving

the matter only passing mention, was the first to recognize the phenomenon of increased cellular resistance to poisons.

Baehr (22) administered small subcutaneous doses of uranium nitrate

- (22) Baehr, George, Über experimentelle Glomerulonephritis, Beiträge zur path. Anat. 55: p. 545-574, 1913.

to ten rabbits and in one noted a considerable proliferation of the glomerular capsular epithelium. When very small quantities were injected directly into the renal artery more uniform results were obtained, leading to proliferation of the epithelium of Bowman's membrane, adhesion to the glomerular tufts and epithelial crescent formation. Tubular damage was slight.

An excellent and thorough study of epithelial regeneration and interstitial connective tissue proliferation in the uranium kidney was made by Oliver (23) in 1915.

- (23) Oliver, Jean., The histogenesis of chronic uranium nephritis with especial reference to epithelial regeneration. J. Exper. Med., 21: p. 425-451, 1915.

Of the many chemical substances other than uranium nitrate which have been used in attempts to provoke chronic renal lesions only a few need be mentioned.

Petroff (24) using the salts of Hg,

- (24) Petroff, Theodor., Ueber die Einwirkung der Metalle auf die Nieren. Inaug. Diss. Würzburg, 1905.

Cu, Zn, Fe, Ag, P. and As., found that when the action was continued for some time there resulted necrosis of the renal epithelium and proliferation of the connective tissue.

Ehrlich (25) and Levaditi (26) by the use of vinyl amine produced defi-

- (25) Ehrlich, Ueber die Zusammenhang von Chemischer Constitution und Wirkung. 1898, cited by Dickson, Arch. Int. Med. 3: p. 384, 1909.  
(26) Levaditi, Experimentelle Untersuchungen über die Necrose der Nierenpapillae, Arch. internat. de Pharmacod., 8: p. 45, 1901, cited by Dickson, Arch. Int. Med. 3: p. 384, 1909.

nite fibrosis of the kidneys in white mice, secondary to localized hemorrhagic necrosis of the papillae.

Ophüls (27) fed lead carbonate to guinea pigs over periods of two to

- (27) Ophüls, W., Experimental chronic nephritis, J. A. M. A. 48: p. 483, 1907.

five months. The lesions, which were very similar in all, consisted in comparatively slight changes in the epithelium of the convoluted tubules and ascending limbs of Henle with some degeneration and desquamation of cells. An active regenerative process in the epithelium was indicated by the occurrence of occasional mitotic figures. Slight interstitial proliferation and small foci of lymphocytes were noted. Lead acetate was administered to dogs in drinking water, and when treated for a sufficient length of time there developed chronic interstitial nephritis, which though not extreme was definite enough to make sure of the process. A few dogs also received potassium bichromate. In a later communication Ophüls (28) expresses the opinion that the lesions in one chromate dog

- (28) Ophüls, W. Some interesting points in regard to experimental chronic nephritis. J. Med. Research. 18: p. 497, 1908.

reported in the previous paper (27)

were evidently spontaneous in origin and is doubtful as to the reality of the changes in two others. In the latter communication (28) appears a statement of great interest because it shows that Ophüls recognized the development of tolerance for renal poisons. In connection with one dog in which the dosage was raised quite perceptibly over a period of sixteen months he says: "The experiments so far show, however, quite clearly that after awhile dogs also will tolerate doses without much injury, which at first would have done them serious damage, if not killed them outright" (p. 506).

Recently Frandsen (29) has reported the production of well marked

- (29) Frandsen, Johannes, Sur les Néphrites Chroniques Experimentales. *Compt. rend. Soc. de biol.* 91: p. 413-415, July 11, 1924.

chronic glomerulo-tubular nephritis in rabbits by the intravenous injection of sodium cantharidate. Other rabbits given potassium bichromate intravenously exhibited marked tubular and glomerular atrophy with great increase in interstitial tissue. Frandsen believes the latter type of nephritis remains a purely tubular one for several months, the glomeruli being affected only in the last stages.

Jessen (30) has recently perfected a technique (hypodermoclysis) by

- (30) Jessen, Jes., Méthode ayant pour but de provoquer des Néphrites Chroniques chez le Lapin. *Compt. rend. Soc. de biol.* 91: p. 1111-1113, Nov. 21, 1924, (illus.)

means of which long continued subcutaneous administration of both inorganic and organic substances in very weak concentration can be carried out

and which he believes produces more uniform results than are obtainable by the usual modes of administration. By this method Jessen (31) has induced a pure tubular nephritis with potas-

- (31) Jessen, Jes., Nye Undersogelser over Kromnefritis, *Hospitaltid.* 68: p. 921, Oct. 1, 1925.

sium chromate in which after a time there was well developed connective tissue and lymphocytic infiltration in the region of the glomeruli and affected tubules. He (32) has likewise given uranyl acetate to rabbits by the drip

- (32) Jessen, Jes., Nye Undersogelser over Urannefritis, *Hospitaltid.* 68: p. 656, 1925.

method. After three months all animals showed regeneration of epithelium in the third and fourth segments of the proximal convoluted tubules with increase of connective tissue and sometimes marked lymphocytic infiltration about the affected tubules. Bing, Heckscher and Jessen (33) found regeneration of cells in the proximal con-

- (33) Bing, H. J., Heckscher, H., and Jessen, J., Studies on the fat-cholesterol contents of the blood in rabbits suffering from an artificial nephritis. *Acta path. et microbiol. Scandinav.* 2: p. 234, 1925.

voluted tubules, together with slight connective tissue proliferation in a rabbit first given uranyl acetate and later phosphorus by hypodermoclysis. Although uranyl acetate was administered to a number of rabbits over periods of several months the total quantity never exceeded 40 milligrams.

The roentgen ray was employed as a means of provoking chronic nephritis as early as 1905 by Schulz and Hoff-

mann (34) but seems to have been for-

- (34) Schulz and Hoffmann, *Deutsch, Ztschr. f. Chir.* 79: p. 350, 1905.

gotten until recently when Hartman, Bolliger and Doub (35), O'Hare and others (36) have revived its use.

- (35) Hartman, F. W., Bolliger, A., and Doub, H. P., *Experimental Nephritis produced by Irradiation. Am. J. Med. Sci.* 172: p. 487-501, Oct., 1926.  
(36) O'Hare, J. P., Altnow, H., Christian, T. D. Jr., Calhoun, A. W. and Sosman, M. C. *Chronic Nephritis produced by X-ray. Boston M. and S. J.* 194: p. 43-45, 1926.

The first named authors (35) found pathological alterations in all kidney structures, the order of severity being interstitial, vascular, and glomerular while the latter (36) describe extensive connective tissue increase, sclerosis of vessels and atrophy of the tubules. Bell, Clawson and Hartzell (37) have produced glomerulonephritis

- (37) Bell, E. T., Clawson, B. J. and Hartzell, T. B., *Experimental glomerulonephritis Am. J. Path.* 1: p. 247, 1925.

in monkeys by repeated intravenous injections of streptococci.

The foregoing review does not include all experimental work on chronic nephritis. Some references which have little value or merit have been omitted. Full and comprehensive discussions of the older literature on the subject will be found in the works of Lyon (38) and Ophüls (27). More recently Mac-

- (38) Lyon, George., *Inflammatory changes in the kidney: an experimental study of the action of some toxins and poisons upon the kidney and also upon the spleen. J. Path. and Bact.* 9: p. 400-456, 1903.

Nider (39) has fully reviewed the lit-

- (39) MacNider, Wm. de B., *A Review of Acute Experimental nephritis. Physiol. Rev.* 4: p. 595-638, 1924.

erature on acute experimental nephritis.

The only authors who have directly mentioned immunity of renal epithelium are Suzuki (loc. cit.) and Gil y Gil (loc. cit.) Since the latter is the only investigator whose research has been wholly concerned with this problem it becomes necessary, on account of the writer having repeated the work, to discuss Gil y Gil's article somewhat in detail.

#### CRITICAL REVIEW.

Gil y Gil states that although a number of research workers have shown that unicellular or higher organisms are capable of developing an immunity for certain substances, the site or morphology of this immunity could not be established. It appeared to him that if immunity of definite cells in higher animals is to be demonstrated, poisons having a direct specific action on these cells must be used. Suzuki's experiments had shown that sublimate and uranium nitrate affect only the epithelium of the proximal convoluted tubules and in some dosages only certain segments of these. Thus the thought occurred to Gil y Gil that with repeated administrations of sufficiently small quantities of poisons the renal epithelium might become tolerant to doses larger than the lethal.

Because of the general action which these poisons also have, the author speaks with caution of the manner in which a local immunity is attained. It appeared to him conceivable that in

repeatedly poisoned animals the uranium might no longer pass through the kidney but be assimilated and excreted by other channels. On account of this possibility it seemed necessary to prove whether or not uranium was excreted by immunized and acutely poisoned kidneys.

Immunization with uranium proved more difficult than with sublimate for after too large or too frequently repeated doses the animals refused food, lost weight and often died. A certain number in his series had only one injection to determine the lethal dose, some died during the course of immunization and only a few could be regarded as successfully immunized. The total number of rabbits employed in the experiments was twenty-four.

Study of the kidney following a single injection of uranium demonstrated that the changes vary according to the quantity given and the duration of time after the injection. In two rabbits regarded as the best examples of immunization there was little or no fresh epithelial damage after dosages capable of evoking very pronounced changes in the normal kidney. This was regarded as proof of tolerance on the part of the epithelium of immunized kidneys.

A number of chemical methods were employed in the hope of determining whether the uranium given was excreted through the kidney or was combined with the tubular cell protoplasm or in other organs, particularly the liver. None gave satisfactory results and were accordingly abandoned.

The formation of uranyl ferrocyanide in a uranium-containing solution by reaction with potassium ferrocyanide

was taken as a basis for the quantitative estimation of uranium in the urine. Unfortunately the method could not be used if iron was also present and for this reason he was unable to obtain any results with the kidney and liver and only rarely with urine since traces of blood were found to be present in most specimens.

Finally a biological method was tried. Urine from uranium rabbits was collected, sterilized and injected intraperitoneally in mice. Tubular lesions having the same localizations as in the rabbits were found.

On two occasions the urine of one immunized rabbit was blood free so that the colorimetric method could be employed. After giving 0.08 gm. subcutaneously, 0.002 gm. was excreted during the first four hours. Following a later intravenous injection of 0.01 gm. it was found that one-half the amount given had passed through the kidney within seven hours. Positive results were also obtained in mice injected with urine from these specimens. A normal rabbit which had received 0.01 gm. intravenously was unable to excrete any uranium in seven hours.

From the experiments Gil y Gil concludes that:

1. It is possible to successfully immunize the kidneys of rabbits against poisoning by uranium and sublimate, so that not only frequent toxic subcutaneous, but also intravenous doses, can easily be tolerated.

2. Uranium acts on the glomeruli as well as the tubular system. One apparatus (tubular) may be immunized while the other still continues to show susceptibility.

3. The various segments of the proximal convoluted tubules are not equally immunized. The most marked action is first in the distal segments, which are also most easily immunized, while the medial and proximal divisions are still distinctly sensitive to larger doses.

4. Proof that parenchymatous injury is actual and not concerned with retention of the poison in other places is shown by excretion of the poisonous material in the urine.

5. Immunization is accomplished by partial destruction of the kidney tissue and leads to the characteristic picture of parenchymatous uranium or sublimate contracted kidney.

It is unnecessary here to discuss Gil y Gil's experiments with mercuric chloride immunization since I have repeated his experiments with this poison, the results of which, together with a review of his work are to be published separately.

#### CRITICISM OF GIL Y GIL'S METHODS AND RESULTS.

1. Inadequate control of experiments. The practical importance of knowing as nearly as possible the onset and duration of cell necrosis, the time of appearance of regenerated cells in the location of those killed by the poison, the rate of progress and the time required for complete regeneration cannot be over-emphasized when applied to a study of immunization of specific cells. In the case of renal tubular cells the question of immunity is wholly concerned with the condition of regenerated epithelium, not the original cells, since these always remain susceptible to injury by large

amounts of a poison and are therefore an unreliable criterion of immunity. Apparently Gil y Gil did not have a clear conception of which renal tubular cells are immunized. He makes no direct reference to the condition of regenerated tubular cells. Suzuki, the first to recognize the phenomenon of increased resistance of renal cells to uranium states specifically that it is the regenerated epithelium which shows no injury. When it is possible to demonstrate histologically that a cell is undamaged by an equal or greater quantity of the substance capable of killing cells originally in the same location, then and only then can we properly speak of specific cellular immunity.

*If one is to be certain what cells were killed by a given injection of poison the examination must be made after unmistakable cellular degenerative changes have had time to develop, while the morphology of the dead cells is still recognizable, and before any or but very slight regeneration takes place.* Unless this rule is invariably adhered to, accurate interpretation of findings is most difficult. It becomes next to impossible to determine whether or not the regenerated epithelium is damaged if the animal is allowed to live until regeneration has taken place in the segments affected by the last given dose of poison, since such new cells will appear exactly the same as those which may have been present for weeks or months previously. Gil y Gil himself asserts that the height of necrosis is attained in five or six days and the inference is that after this the action recedes. How then is it possible to allow animals to live until regeneration must be well

advanced, until the destructive process is past its zenith, and then assert, as he does, that immunity is proven by lack of injury to the kidney epithelium? Examining the protocols of his immune series we find that:

Rabbit J-18	killed	11	days	after	last	injection
" J-19	"	9	"	"	"	"
" J-20	"	7	"	"	"	"
" J-21	"	1	"	"	"	"
" J-22	"	5	"	"	"	"
" J-23	"	10	"	"	"	"
" J-24	"	1	"	"	"	"

It is thus evident that he either considered the length of time after an injection unimportant or in most instances wholly overlooked its importance. Yet if we turn to the records of his non-immunized animals it will be seen that regeneration was found fairly constantly after six days. Whether he believed that no regeneration would take place after administrations of large amounts of uranium and was thus safe in allowing life to continue for as long as eleven days cannot be determined from the text of the article.

No claim of immunity is made for Rabbits J-18, 19, 20 and 22. In J-21 he speaks of glomerular but not tubular immunity. But in this animal hyaline droplet degeneration in the glomerular capillaries is described as abundant, a change which in another place he attributes to the injurious effect of uranium. Such contradictions and ambiguities do not strengthen the proof of immunity.

Rabbits J-23 and 24 were regarded as the best examples of immunization. It will be noted however that J-23 was not studied until *ten days* after the last injection. To say as he does "Bemerkenswert ist, das diese

Schrumpfnieren trotz der wiederholten schweren Vergiftungen gar keine frischen Nekrosen zeigt, auch keine frischen Affektionen der Glomeruli" proves absolutely nothing because in such a long interval there was ample time for subsidence of injury and for almost complete relining of the damaged tubules by new epithelium, which of course would show no evidence of injury.

2. Subcutaneous and intravenous administrations in the same immune animal.

This should never be done unless the relative ratio in effect between subcutaneous and intravenous doses has been determined. Gil y Gil failed to do this, yet in Rabbit J-24 after subcutaneous administrations up to 80 milligrams, gave intravenous injections, the largest of which was only 10 milligrams, killed the animal a day later, and, finding no fresh lesions, counted this animal the best example of immunization. More convincing proof would be offered had increasingly larger subcutaneous doses been given.

3. Inadequate determination of the lethal dose. At the outset the author states that the factors to be considered in this determination are: (a) use of healthy animals of equal weight, (b) a given time in which death must occur and (c) extrarenal factors. In fairness it must be said he admits that on this basis the lethal dose will be only approximately correct, varying within narrow limits. As to these limits or what the lethal dose was found to be nothing is said. Animals given the same quantity of uranium frequently differed considerably in weight. There is little or no discus-

sion of extrarenal factors. Of the nine rabbits receiving 0.001 gm. subcutaneously more than one-half survived. Two milligrams administered in the same way killed two-thirds of the animals. The smaller number of rabbits given intravenous injections and the wide differences in the amount administered makes impossible any conclusion as to the quantity necessary to cause death when injected in this way.

#### AUTHOR'S EXPERIMENTS.

##### 1. *General Considerations of the Problem of Cellular Immunity.*

In attempting to demonstrate immunity of specific cells for a poison the experimental worker must clearly differentiate between (1) the *fact* or *proof* of immunity and (2) the *mechanism* or *means* by which this phenomenon is made possible.

In (1) the factors involved and procedure to be followed are relatively simple. First, certain criteria of immunity must be established. Of the several possibilities three are at once apparent, namely:

(a) Immunization of the organism as a whole. Here the first step is clearly that of establishing the minimum lethal dose, taking into consideration such factors as individual differences in susceptibility, mode of administration of the poison, weight, age, sex and the presence of complicating disease processes. The number of times the minimal lethal dose which the animal is able to withstand will then indicate the degree of tolerance or immunity attained.

(b) Specific or local cellular immunity. This is of the greatest importance if it can be proven to exist. Fortunately we have in the salts of the heavy metals, particularly of uranium, chromium and mercury, substances which act selectively on certain divisions of the proximal convoluted tubular system producing sharply demarcated and easily recognizable lesions which are ideal for the study of local immunity. That the selective site of injury by uranium is in the distal and transitional parts of the proximal convoluted tubules is readily proven by intravital staining with carmine. Suzuki (21), Möllendorff, (40) and Mitamura (41) have shown that carmine is taken up in varying amounts

(40) Möllendorff, W., Vitale Färbungen an tierschen Zellen, *Ergebn. d. Physiol.* 18: p. 141, 1920.

(41) Mitamura, Tokushiro., Neue Belege zur Ludwig-Cushnyschen Filtrations theorie der Niere (Vorläufige Mitteilung) *Pflüger's Arch. f. Physiol.* 204: p. 561-571, 1924.

by the different segments of the proximal convoluted tubules. When the epithelium in any division is destroyed there is no longer a characteristic arrangement of carmine granules in the dead cells thus definitely localizing the lesion. If after allowing sufficient time for cellular regeneration in the affected tubular segments the animal is intravitaly stained with carmine it will be noted that the new cells are unstained by the dye, a fact first pointed out by Ribbert (42) and later confirmed by

(42) Ribbert, H., Die Abscheidung intravenös injizierten gelösten Karmins in den Geweben, *Ztschr. f. allg. Physiol.* 4: p. 201-214, 1904.



Oliver (23). The latter procedure although a valuable aid in the recognition of regenerated epithelium is not absolutely essential since the new cells present permanent alterations in histologic and staining qualities which readily distinguish them from original epithelium.

Assuming that the poison is always excreted by the kidney irrespective of the dosage or the pathologic condition of the organ, all that is necessary to prove immunity after establishing the site of injury and the smallest quantity required for constant production of cellular damage, is to allow sufficient time between injections for complete regeneration of cells, increase the dosage and demonstrate that the new cells are uninjured. Using this criterion the degree of cellular immunity may be expressed in multiples of the amount known to kill the original cells in the same location.

(c) Ability of the kidney to excrete a given amount of uranium.

Other factors which must be kept in mind without regard to the criterion used for immunity are:

(a) The possibility of cumulative action. Whether this occurs or not it is essential that the animal be given the opportunity of recovering as fully as possible from the effects of one injection before administering another.

(b) Complications and difficulties in determining the degree of tolerance attained may be avoided by administering the poison wholly subcutaneously or intravenously in any given animal.

(2) Mechanism of the immunity. Many difficult questions are encountered when one attempts to explain

the means by which the immunity is accomplished.

Does the substance injure the body as a whole, several organs or systems, or but a single structure? If small quantities are found to affect only the kidney, is the same true for larger doses?

In the case of the kidney numerous questions intimately concerned with the nature and mechanism of renal function arise. The modern view of Cushny, (43) amply confirmed by the recent experimental work of Wearn and Richards (44) is today generally accepted as the best explanation of

(43) Cushny, A. R., *The Secretion of the Urine*, Longmans, Green and Co., London, 1926.

(44) Wearn, J. T. and Richards, A. N., *Observations on the composition of glomerular urine, with particular reference to the problem of reabsorption in the renal tubules*. *Am. J. Physiol.* 71: p. 209, 1924.

renal secretion. According to this theory the function of the glomeruli is that of filtration—a purely physical process, while that of the tubules is re-absorption in which the vital activity of the tubular epithelium is assumed to have a part. Uranium must reach the kidney by way of the blood stream and if Cushny's view is accepted the glomeruli are first to come in contact with it. Does part or all of the uranium pass through the glomeruli and exert its effect at the point of selective re-absorption in the proximal convoluted tubules or are the glomeruli also injured? If so what is the effect—immunity with more ready excretion or on the contrary retardation or even inhibition? What is the chemical nature of the injury? Is

the poison held in combination with cell protein? Does regenerated epithelium become tolerant or resistant to the poison rendering re-absorption impossible, or on the other hand are the new cells capable of incorporating and detoxicating it? These questions will be dealt with later in the discussion of results.

## 2. *Material and Methods.*

In order to have a basis for comparison of results with those of Gil y Gil the rabbit was selected as the experimental animal.

It appeared necessary first of all to determine the lethal dose of uranium for this animal. Healthy rabbits of both sexes were used, most of which were full grown although a few small and apparently young ones were included. The importance of weight was found to be negligible and in the immunization series no particular attention was paid to it.

A few animals in each subcutaneous and one intravenous series were killed 1 and 3 days after injection to study the evolution of the kidney lesions. Two were intravitaly stained with carmine for the purpose of localizing the tubular lesions. Complete necropsies were done in all cases.

In addition to establishing the lethal dose, animals dying from the effect of kidney damage served the useful purpose of following the progress of the lesion over a period of a week or more, thus enabling one to determine when the necrosis reached its zenith and also to study the early stages of epithelial regeneration.

Autopsies were done as soon as possible after death and the tissues placed

immediately in both Zenker-formol and formalin. In practically every instance the following stains were employed: hematoxylin-eosin, van Gieson, Mallory's phosphotungstic acid hematoxylin (for hyaline droplet degeneration), potassium ferrocyanide-carmine for iron and Scharlach-R for fat. The kidneys of intravitaly stained animals were fixed in formalin, imbedded and cut in the usual manner and counter-stained for 20-30 seconds in hematoxylin.

Rabbits were caged throughout the course of the experiments and kept on a diet consisting of oats, hay, carrots and vegetable trimmings.

In the immunization series the interval between injections was governed partly by the time found necessary for complete regeneration of epithelium (14 days) and in part by the condition of the animals. It was soon found that the animals reacted much better if a twenty-one rather than a fourteen-day interval was allowed and for the greater part of the time this was adhered to as nearly as practicable.

Chemically pure uranium nitrate (Mallinckrodt)  $\text{UO}_2(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  was used. The solutions injected were freshly prepared before each injection, dissolving the crystals in sterile distilled water, at first in the strength of 0.001 gm. of uranium nitrate (including the water of crystallization) to 1 cc. of water. Later as the doses were increased the concentration was raised to 0.002, 0.004 and finally 0.008 gm. per cubic centimeter of solvent. None of these solutions were strong enough to cause local irritation at the site of injection.

### 3. *The Minimum Lethal Dose.*

#### (I) Subcutaneous injection.

(a) 0.001 gm. was administered to 33 rabbits varying in weight from 1570 to 3035 gms. Twenty-eight (90.32 per cent) survived, three (9.67 per cent) succumbed within 4-5 days, two were killed for study before three days had elapsed and are not included.

(b) 0.002 gm. Twelve rabbits weighing from 1275 to 2700 gms. received this quantity. Two were killed 1 and 3 days later and are therefore excluded, nine (90 per cent) died between 5 and 13 days after injection. With one exception all deaths occurred between 5 and 7 days. Only one rabbit (10 per cent) survived.

The percentage of animals killed by 0.001 gm. is negligible. On the other hand 0.002 gm. proved fatal in 90 per cent of cases and may therefore be regarded as the subcutaneous minimum lethal dose.

#### (II) Intravenous injection.

(a) 0.0005 gm. Of the 24 animals given this dose only one failed to survive.

(b) 0.001 gm. was administered to 6 rabbits. Two were killed for study within three days. The four remaining died between  $3\frac{1}{2}$  to 4 days after injection. The weights of this group varied from 1000 to 1500 gms.

(c) 0.002 gm. given to two rabbits, each weighing 1400 gms. produced death within three days.

These results show that 0.001 gm. of uranium intravenously constitutes the minimum lethal dose for rabbits.

### 4. *Acute Uranium Nephritis.*

In order to fully understand the changes observed in the chronic immunized uranium kidney it is necessary first to describe the acute phase of the lesion. Lack of space forbids describing individual cases but it is possible to make a composite description giving the essential changes shown in all acute uranium kidneys. The intensity and extent of the lesions naturally varies with the quantity given, the manner of administration, and the time after injection when the kidney is examined.

It may be stated as a general rule that after a small subcutaneous dose, e. g., 0.001 or 0.002 gm., actual necrosis occurs only in the distal and transitional segments of proximal convoluted tubules, particularly the former, and that the involvement will be rather sharply limited to those tubules situated in the inner part of the cortex. With larger doses however the damage is more extensive, extending into the medial segment of the tubules and spreading into the intermediate and outer cortical zones.

At the end of the first day after administration of a small dose there is very little actual necrosis of epithelium in the segments for which uranium has a specific affinity, although many appear slightly swollen, more granular than normal and their nuclei may exhibit beginning pyknosis or karyolysis. Only a few will be found desquamating into the lumen. The glomerular capillaries are frequently congested, reducing the size of the capsular space. Even at this early stage there is not infrequently a perceptible swelling of

the cytoplasm of the glomerular and Bowman's membrane epithelium.

After three days the cells in the distal and transitional divisions are mostly necrotic. With small doses the necrosis is of the simple type but with larger amounts all dead cells may fuse into hyalin-like homogeneous masses adherent to the basement membrane and almost closing the lumina. The dead cells are seen either partly or wholly detached from the basement membrane and forming loose masses in the lumen. Their cytoplasm is swollen and often thickly set with fine vacuoles which in Scharlach-R preparations prove to be fat. Most nuclei are markedly pyknotic and in varying stages of extrusion from the cell body, others show karyolysis or karyorrhexis and becoming mixed with the dead cellular debris. Not all cells in the affected segments are killed. There always remains here and there a cell or two which though definitely altered in appearance remains alive and attached to the basement membrane. It is from such cells that regeneration largely occurs. Even with large doses the first division of the proximal convoluted tubules remains alive, the cells exhibiting varying degrees of parenchymatous degeneration but rarely necrosis. No perceptible injury is to be detected in the other tubular systems.

The origin of casts and their morphology in the various parts of the tubular system is of interest. The dead epithelium in the affected segments first lies loosely in the lumen but on passing into the descending limb of Henle's loop all form of cell outline is lost, the detritus becoming compact and homogeneous. Although most casts are

of this type it is not uncommon to find a few epithelial cells with pyknotic nuclei included in the masses, also nuclear fragments and varying numbers of red blood cells. Most casts contain rounded or oval vacuoles which prove to be fat when stained with Scharlach-R. By the third day the number of casts is enormous, filling nearly all tubules in the cortical medullary rays. Undoubtedly the albuminous material from the glomerular capsular spaces contributes to the formation of casts but certainly the greater part comes from tubular epithelium.

With larger doses glomerular changes become more pronounced, showing either congestion of the capillaries or a filling of the lumina with what appears to be fibrin. The cytoplasm of the cells covering the tufts and Bowman's membrane becomes swollen and granular and not infrequently the cells desquamate into the capsular space forming finely granular masses. Adhesions between the tuft and capsule at one or more points are often seen. Another important lesion occurring in some animals even after very small subcutaneous or intravenous doses is destruction of one or more divisions of the glomerulus with the formation of cyst-like intraglomerular hemorrhages. Less commonly the entire glomerulus is thus destroyed. Whenever such hemorrhages are present some capsular spaces will be found filled with well-preserved red blood cells and in the proximal convoluted tubules pure blood casts may be very numerous. The later stages of these hemorrhagic glomerular lesions are not often observed. In some instances the entire glomerulus disappears and

the space is filled with fibrin and blood, in others where but one or two divisions of the tuft are involved healing takes place by organization of the hemorrhage.

That uranium nitrate injures the glomeruli cannot be doubted. Even when only slight alteration is demonstrable in the covering epithelium careful search will nearly always reveal a few red blood cells in the capsular spaces. This occurs so constantly that it is difficult to believe it could be due to artefact. The cells must escape by diapedesis made possible through injury of the capillary endothelium. Albuminous material in the capsular space also speaks for glomerular damage. The more definite changes such as necrosis and desquamation of epithelium have been mentioned. Sections of the acute uranium kidney fixed in Zenker's fluid and stained with Mallory's phosphotungstic acid hematoxylin show in a considerable proportion of cases the hyaline droplet degeneration, first described by Christian (45) who regarded this change as evidence

(45) Christian, H. A. A Glomerular lesion of experimental nephritis. Boston M. and S. J. 159: p. 8, 1908.

of glomerular capillary injury. These droplets are rounded bluish-black stained bodies occurring in groups of three to twelve or more within the capillary endothelial cells.

Increase of wandering cells, chiefly lymphocytes, is usually slight during the acute stage of uranium nephritis. Edema of the interstitial tissue and pelvic fat is quite constantly found.

The height of the destructive process is reached about the fifth day

after which time only occasional cells are lost, the injured but viable epithelium regains its normal appearance while casts diminish in number until by the end of 10-14 days very few still remain in the tubules.

#### REGENERATION OF EPITHELIUM.

In rabbits I have never observed regeneration earlier than the fourth day after injection but on the fifth day there is always unmistakable evidence of regenerative activity. At this time although most tubules are still filled with granular debris and the membrana propria is for the most part bare, there will be seen varying numbers of large oval nuclei containing a considerable amount of loosely arranged chromatin with one or two nucleoli. Covering these nuclei is a thin layer of bluish staining cytoplasm which may be seen pushing along the barren basement membrane and often blending imperceptibly with that of other new cells. In other places the rapidly proliferating epithelium forms syncytial giant cells which project irregularly into the lumen. Among the obviously new-formed cells others having nuclei about the size of normal renal cells and staining very deeply with hematoxylin will be found. There is much evidence to show that these are original tubular cells which, although injured are still viable and the not infrequent pre-mitotic and mitotic figures strongly indicate that from these much of the regenerated epithelium is formed. As time advances the membrana propria is covered over by new cells derived from mitosis of previously existing single cells and extension of the syncytial giant-cell protoplasm with enclosed

nuclei. There is often an over-production of cellular elements so that the regenerated epithelium no longer consists of a single layer but of irregularly densely packed cells in palisades or more frequently in rows two or three deep. By the end of the fourteenth day regeneration is nearly complete. The alteration in size, shape, staining qualities and arrangement of the new epithelium is permanent.

Phagocytosis of necrotic cell material by regenerated epithelium is, in my experience, a fairly common occurrence. Regeneration begins even while the lumina are filled with granular debris and the protoplasmic processes of the new cells push between the granules engulfing and incorporating them within the cytoplasm. The process is readily recognized on account of the striking difference in the staining of the debris and new cell cytoplasm. The possible fate of this debris will be discussed later.

#### CONNECTIVE TISSUE PROLIFERATION.

The denuded basement membrane remains inactive for several days in the stage of the acute lesion but after five to seven days begins to show signs of activity in the form of increase in size and number of cells which may at times project into the lumen of the tubule. At the same time the intertubular connective tissue cells are rapidly proliferating but in the rabbit rarely grow into the lumina. Dilatation of the tubules proximal to the seat of injury is not the result of occlusion of tubules by necrotic material because this is not present in the early stages but begins only with the proliferation of connective tissue and increases in direct proportion to it.

With repeated injections of increased amounts of uranium there is a repetition of all stages of the acute process. The localization which at first is in the inner cortex is now found in patches scattered irregularly throughout the intermediate and outer cortical zones. With increased dosage the medial segments of proximal convoluted tubules are killed but this is rarely the case with the first divisions. As the tubular epithelium is gradually destroyed and replaced by new cells the accompanying connective tissue increase likewise becomes more extensive, producing marked distortion of histological pattern. Contraction of the scar tissue of the subcortical zone gives rise to the finely granular surface of a typical secondary contracted kidney. On cut section the chronic uranium kidney constantly presents a definite line of scar tissue at the cortico-medullary boundary and extending irregularly outward toward the capsule.

#### 5. Immunization Experiments.

After having determined that 0.001 gm. subcutaneously and half this quantity intravenously constantly kills original renal tubular cells, but not the animal, the next step was to begin with these doses and by gradually increasing the amount attain the highest degree of tolerance possible.

Table 1 shows the general plan followed in each series, the total number of animals and those in each group showing immunization. Animals living long enough after the last injection for regenerative changes to take place have without exception been excluded. Likewise a number of rabbits which survived only the first few doses, even

though some had well developed chronic nephritis and exhibited no evidence of injury to regenerated epithelium have been omitted because the degree of immunity was not great enough to be of much value.

Tables II and III give the essential data in all successfully immunized rabbits. With the exception of the two groups in which an attempt was made to repeat Gil y Gil's experiments a definite plan of increasing the dosage was followed. In the series in which the doses were increased by doubling each previous amount, it was apparent that this could not be carried too far and for this reason the later doses

correspond to one-fourth or one-half of the computed amount of double the last dose.

The large number of animals makes it impossible to describe each in detail but since all are essentially alike, differing only in unimportant details, the description of a few will suffice.

*Rabbit 4-A.*

*Gross Examination.*—Weight 2770 gms. Slight edema of subcutaneous tissue at site of last injection. Body nourishment good. No ascites or hydrothorax. Urinary bladder contains 2 c. c. of cloudy urine. On section the liver is soft, friable, and distinctly fatty.

TABLE I.—General plan of increasing dosages in the various immunization groups.

Series	Method of Administration	Method of increasing doses	Number rabbits in series	Number regarded as immune	Number not included in immune series
A	Subcutan.	doubling each previous dose	13	5	7
	Subcutan.	tripling each previous dose	6	0	6
GyG	Subcutan.	as in GyG Rabbit J.23	6	0	6
	Subcutan. and Intraven.	as in GyG Rabbit J.24	11	2	9
B	Intraven.	doubling each previous dose	18	6	12
	Intraven.	tripling each previous dose	6	4	2
			60	17	42

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TABLE II.—Essential data of animals in Immunization series A and GyG.

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
4-A	2400	5-18-26	0.001	Subcut	D	2	226
	2000	6- 1-26	0.002	"			
	2250	6-15-26	0.004	"			
	2050	7- 6-26	0.008	"			
	2120	7-27-26	0.016	"			
	2300	8-17-26	0.032	"			
	2360	9- 7-26	0.064	"			
	3050	12- 7-26	0.080	"			
	2840	12-28-26	0.096	"			
5-A	2600	5- 4-26	0.001	"	D	2	128
	2750	5-18-26	0.002	"			
	2350	6- 1-26	0.004	"			
	2550	6-15-26	0.008	"			
	2400	7- 6-26	0.016	"			
	2420	7-27-26	0.032	"			
	2525	8-17-26	0.064	"			
	2665	9- 7-26	0.096	"			
9-A	2500	5-18-26	0.001	"	D	2	157
	2000	6- 1-26	0.002	"			
	2150	6-15-26	0.004	"			
	1690	7- 6-26	0.008	"			
	1830	7-27-26	0.016	"			
	2225	8-17-26	0.032	"			
	2380	9- 4-26	0.064	"			
	2300	9-28-26	0.080	"			
	2290	10-19-26	0.096	"			
11-A	2300	5-18-26	0.001	"	D	2	114
	2000	6- 1-26	0.002	"			
	2075	6-15-26	0.004	"			
	2070	7- 6-26	0.008	"			
	2325	7-27-26	0.016	"			
	2370	8-17-26	0.032	"			
	2470	9- 7-26	0.064	"			
12-A	2300	5-18-26	0.001	"	D	3	115
	1900	6- 1-26	0.002	"			
	2175	6-15-26	0.004	"			
	2100	7- 6-26	0.008	"			
	2400	7-27-26	0.016	"			
	2385	8-17-26	0.032	"			
	2365	9- 7-26	0.064	"			



TABLE II—CONTINUED

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
14-GyG J.24	2500	6-16-26	0.001	"	D	8-20 hr	62
	1970	7- 6-26	0.008	"			
	2265	7-27-26	0.030	"			
	2290	8-17-26	0.080	"			
15-GyG J.24	2400	6-16-26	0.001	"	K	2	127
	2170	7- 6-26	0.008	"			
	2285	7-27-26	0.030	"			
	2400	8-17-26	0.080	"			
	2365	9- 7-26	0.002	Intraven			
	2530	9-28-26	0.035	"			
	2515	10-19-26	0.010	"			

TABLE III.—Essential data of rabbits in Immunization series B.

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
BAI-B	2400	5-22-26	0.0005	Intraven	D	2	149
	2000	6- 1-26	0.001	"			
	2250	6-16-26	0.002	"			
	2075	7- 3-26	0.004	"			
	2420	7-24-26	0.008	"			
	2560	8-14-26	0.016	"			
	2730	9- 4-26	0.024	"			
	2850	9-25-26	0.032	"			
	2690	10-16-26	0.040	"			
BCI-B	1600	6- 5-26	0.0005	"	K	3	199
	1600	6-19-26	0.0005	"			
	1450	7- 3-26	0.001	"			
	1600	7-24-26	0.002	"			
	1820	8-14-26	0.004	"			
	2005	9- 4-26	0.008	"			
	2210	9-25-26	0.015	"			
	2310	11-27-26	0.024	"			
	2250	12-18-26	0.032	"			

TABLE III—CONTINUED

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
BGI-B	1500	6- 5-26	0.0005	"	K	1½	227½
	1600	6-19-26	0.0005	"			
	1550	7- 3-26	0.001	"			
	1785	7-24-26	0.002	"			
	2020	8-14-26	0.004	"			
	2135	9- 4-26	0.008	"			
	2240	9-25-26	0.016	"			
	2475	11-27-26	0.024	"			
	2250	12-18-26	0.032	"			
	1770	1- 3-27	0.040	"			
	1850	1-17-27	0.048	"			
BJI-B	1650	6-19-26	0.0005	"	K	3	122
	1500	7- 3-26	0.001	"			
	1680	7-24-26	0.002	"			
	1850	8-14-26	0.004	"			
	1725	9- 4-26	0.008	"			
	1720	9-25-26	0.016	"			
	1370	10-16-26	0.024	"			
BLI-B	1500	6-19-26	0.0005	"	D	1	162
	1550	7- 3-26	0.001	"			
	1810	7-24-26	0.002	"			
	2065	8-14-26	0.004	"			
	2210	9- 4-26	0.008	"			
	2400	9-25-26	0.016	"			
	2390	10-16-26	0.024	"			
	2560	11- 6-26	0.032	"			
	2560	11-27-26	0.040	"			
BQI-B	1350	7- 3-26	0.0005	"	D	1	148
	1640	7-17-26	0.001	"			
	1985	8-14-26	0.002	"			
	2100	9- 4-26	0.004	"			
	2450	9-25-2	0.008	"			
	2430	10-16-26	0.016	"			
	2710	11- 6-26	0.024	"			
	2630	11-27-26	0.032	"			
BSI-B	1240	7-17-26	0.0005	"	D	3	101
	1160	7-31-26	0.0005	"			
	1270	8-21-26	0.001	"			
	1430	9-11-26	0.003	"			
	1490	10- 2-26	0.009	"			
	1450	10-23-26	0.027	"			

TABLE III—CONTINUED

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
BTI-B	1510	7-31-26	0.0005	"	K	2	108
	1450	8-21-26	0.0005	"			
	1680	9-11-26	0.001	"			
	1530	10- 2-26	0.003	"			
	1450	10-23-26	0.009	"			
	1400	11-13-26	0.027	"			
BWI-B	1730	7-31-26	0.0005	"	K	3	130
	2000	8-21-26	0.0005	"			
	2380	9-11-26	0.001	"			
	2380	10- 2-26	0.003	"			
	2500	10-23-26	0.009	"			
	2490	11-13-26	0.027	"			
	2220	12- 4-26	0.036	"			
BXI-B	1580	7-31-26	0.0005	"	K	3	109
	1320	8-21-26	0.0005	"			
	1590	9-11-26	0.001	"			
	1620	10- 2-26	0.003	"			
	1720	10-23-26	0.009	"			
	1720	11-13-26	0.027	"			

*Kidneys.*—Combined weight 17.5 gms. Capsules definitely adherent to parenchyma and strip with slight but obviously increased difficulty exposing surfaces which are finely and diffusely granular, brownish in color with many light yellowish-brown pin-point-sized areas raised above the surrounding parenchyma. The organs cut with some difficulty, the cut surfaces show total obliteration of the normal markings in the cortex with here and there fine white scars, particularly marked at the cortico-medullary boundary.

*Microscopic.*—Everywhere in the cortex there is marked diminution of proximal convoluted tubules retaining the original epithelium and in these marked alteration is noted, consisting

of all gradations from parenchymatous and fatty degenerative infiltration to complete necrosis and desquamation. The nuclei are for the most part pyknotic but some show karyorrhexis or karyolysis. Some cells are still viable. There is no evidence of beginning regeneration in these locations.

Many proximal convoluted tubules are lined by typical appearing regenerated epithelium, irregular, often flattened and with dark bluish-pink staining cytoplasm and oval hyperchromatic nuclei. In the cytoplasm of some of these cells there is yellowish-brown granular pigment. Pigment is also found in the lumina of regenerated tubules, particularly those with very small lumina. That some regenerated

tubules are patent and connected with the damaged proximal segments is shown by the presence of desquamated epithelium recognizable as original cells. Hyaline droplet degeneration occurs in some original tubular cells but not in the regenerated epithelium. Very rarely is there any demonstrable

strands resembling amorphous phosphates of the urine are seen.

*Glomeruli.*—There is wide variation in size, some being four or five times larger than others. The hypertrophied glomeruli are well filled with blood. A moderate degree of cystic dilatation of the capsular spaces is frequently

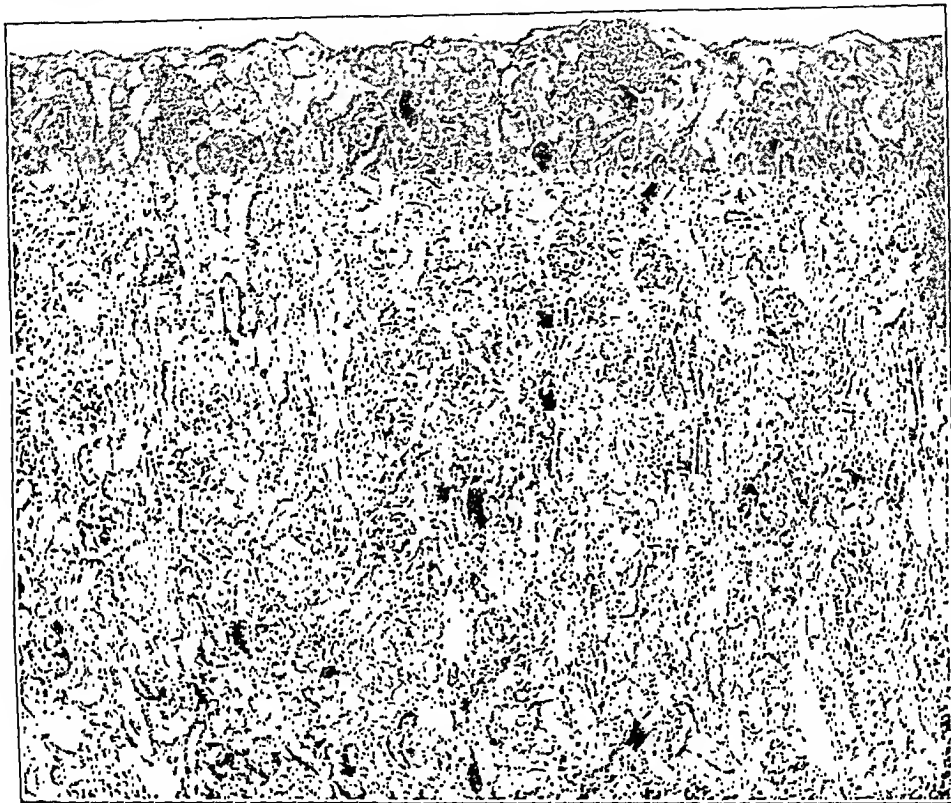


FIG. 1.—Low power photomicrograph of entire kidney cortex showing extent and distribution of lesions on the sixth day after subcutaneous injection of 0.009 gm. uranium nitrate. Necrosis of epithelium in distal and transitional divisions of proximal convoluted tubules in all zones of cortex. Many casts still present.

histological evidence of injury in the regenerated cells. The epithelium of other tubular systems is uninjured. A striking feature is the marked dilatation of the tubules in the cortical rays. Casts are not numerous. Those present are predominantly of the mixed hyaline-fatty-epithelial variety, while in many collecting tubules ropy beaded

observed and in these dilated spaces there is usually some finely granular or homogeneous pinkish staining material. No intraglomerular hemorrhages are present nor are red blood cells found in the glomerular spaces. Increase in number of cells of Bowman's membrane is the rule, varying in degree from slight to very pronounced

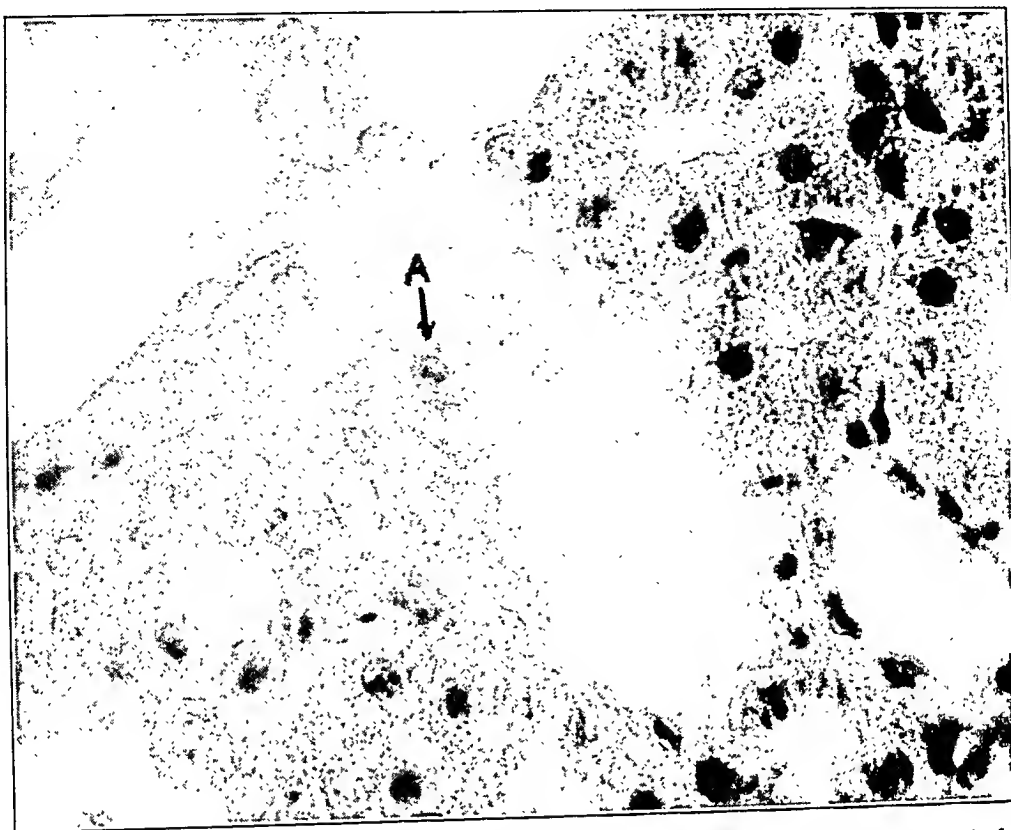


FIG. 2.—Oil immersion. Rabbit 3-A. Last injection of uranium four days before death. At 'A' is an original proximal convoluted tubular cell, which, although injured, is still viable. It is from such cells that regeneration of epithelium largely takes place.

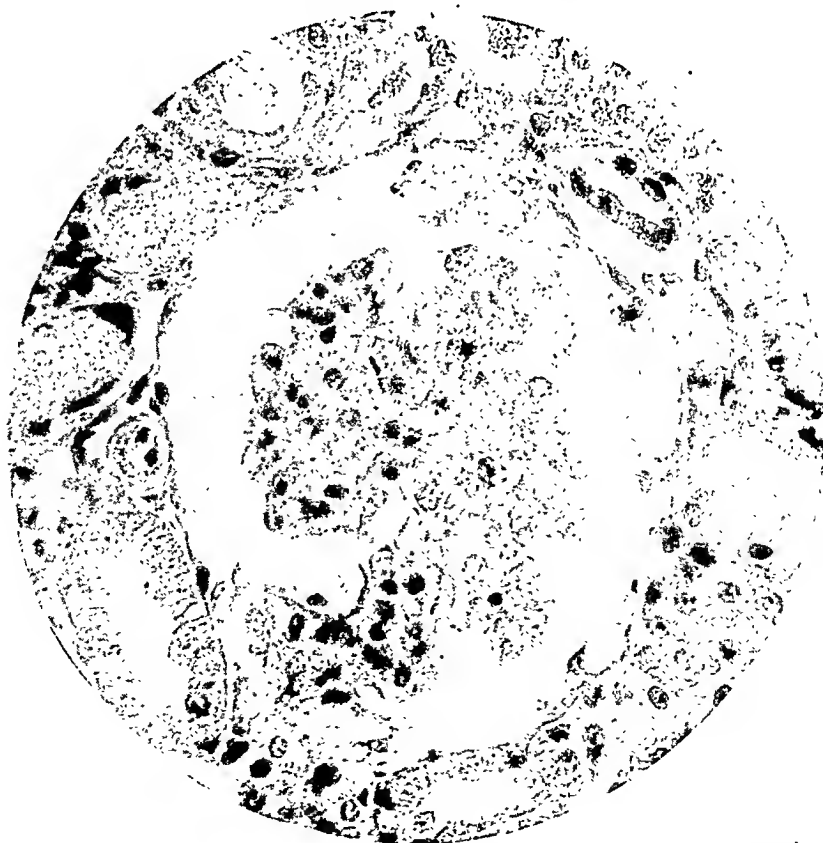


FIG. 3.—Oil immersion. Glomerular damage after 0.009 gm. of uranium subcutaneously. Bowman's membrane epithelium is markedly edematous and some of the cells are undergoing necrosis. The same is true of the covering epithelium of the tuft.



FIG. 4.—Rabbit 23-GyG-J-23. High power. Two milligrams uranium nitrate subcutaneously; death on fifth day. Recent large intraglomerular hemorrhage with destruction of most of the tuft. Strands of fibrin are seen within the clot. At 'A' is a convoluted tubule plugged with red blood cells.

and often forming epithelial crescents which contain vacuoles. Adhesions between the crescents and the glomerular tufts often occurs while glomeruli in which the capsular space is entirely obliterated by a concentric overgrowth of Bowman's membrane epithelium are not rare. Such glomeruli are atrophic and have collapsed and empty vessels. Hyaline droplet degeneration is found in only two of one hundred glomeruli examined.

Van Gieson's preparations show very pronounced interstitial scarring everywhere in the cortex and at the border zone between cortex and medulla, fully as marked in the labyrinths as in the rays. A few small collections of lymphocytes may be seen in the interstitial tissue. The changes occurring in and about the glomerular capsules are best studied with this stain. It is seen that the proliferating epithelium of Bowman's membrane



FIG. 7.—Rabbit 20-GyG-J-23. Oil immersion. 'A' is a segment of proximal convoluted tubule almost fully relined by new epithelium within five days after the administration of 0.002 gm. of uranium. The new cells are flattened and have oval hyperchromatic nuclei; a mitotic figure is seen along the right border. At this point the section is cut through the tubule wall giving the impression that some of the cells are within the lumen. 'B' indicates a proximal convoluted tubule retaining the original epithelium. 'C' is also a division of a proximal convoluted tubule in which the epithelium has been destroyed by the uranium and in which there is as yet no regenerative activity.

ing well preserved red blood cells or blood pigment. Mallory's stain reveals moderate numbers of coarse round droplets in many original proximal convoluted tubular cells. Fat is likewise present in these cells, in the smaller collecting tubular epithelium and abundantly in some casts but only rarely in the regenerated cells.

*Glomeruli.*—Cystic dilatation of the capsular spaces is striking, particularly toward the inner cortex where the scarring is most marked and where there is little regeneration of tubular epithelium. The dilatation is often extreme and in these instances the glomeruli are atrophic and sometimes flattened out along the capsule. In nearly

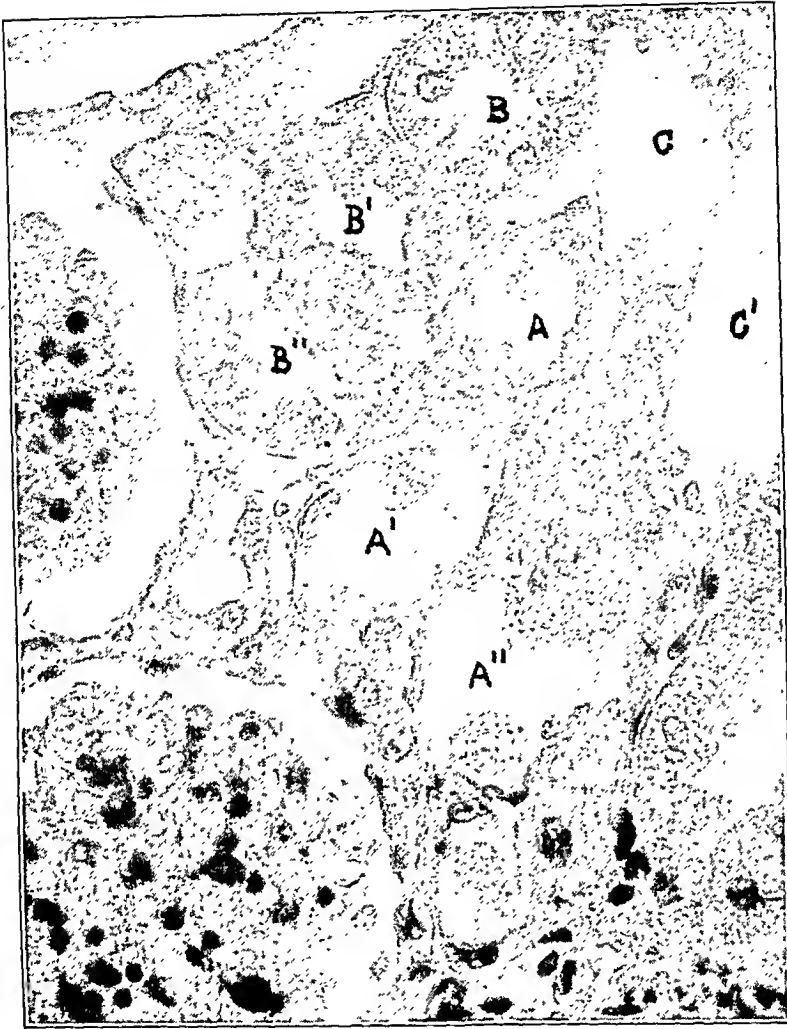


FIG. 8.—High power photomicrograph from same kidney shown in Fig. 7. Several cross-sections of proximal convoluted tubules (A, A', A'') are partially covered by new epithelium. B, B', B'' are uninjured segments of the same tubule. At C and C' regeneration has not started. The striking difference in histologic characteristics of the new and old epithelium is very apparent. In the tubular lumina and glomerular capsular spaces are a few necrotic epithelial cells.

all the marked cystic spaces there is pinkish staining material, rarely a few red blood cells or desquamated epithelial cells. Proliferation of Bowman's epithelium is slight except in rare instances where two or three layers of cells form an epithelial crescent. No instances of complete obliteration are found. Hyaline droplet degeneration of the glomerular capillaries is lacking.

Van Gieson's stain discloses extensive interstitial connective tissue increase in all parts of the cortex. The adventitia of most arcuate and interlobular arteries is increased and directly continuous with the intertubular scarring. The usual iron-free pigment occurs in regenerated epithelial cells.

*Liver.*—Necrosis of an occasional hepatic cell near central veins. No



fatty degenerative infiltration. Slight chronic pericholangitis.

*Rabbit BGI-B.*

*Autopsy Findings.*—Poorly nourished, weight 1800 gms. No subcutaneous edema, hydroperitoneum or hydrothorax. Two cubic centimeters of urine in bladder. Several small consolidations in left lung, also purulent bronchitis. Liver is distinctly fatty.

*Kidneys.*—Combined weight 10 gms. visibly decreased in size. Capsules slightly adherent to parenchyma. Cortical surface finely granular throughout. Definitely increased resistance encountered on sectioning. Cut surfaces show cortex thinner than normal and thickly set with fine whitish scars, normal markings entirely lacking.

*Microscopic.*—The very extreme chronic nephritis in this animal compares favorably with that in the subcutaneous series receiving the largest injections and living the same length of time. Scarring and distortion in the cortex is so extreme that it is practically impossible to recognize the labyrinths and rays. Proximal convoluted tubules with original epithelium are very rare but when found exhibit slight evidence of injury. Many regenerated tubules may be seen in the cortex and the epithelium of these is quite intact. Casts are not numerous. Granular pigment occurs in the cytoplasm of new epithelial cells and in the lumina of regenerated tubules. Preparations stained for fat show this substance in the persisting original convoluted tubular cells, the ascending limbs of Henle and very abundantly in the casts.

*Glomeruli.*—Because of the extensive scarring and subsequent contrac-

tion the glomeruli are numerous in every microscopic field. Many are markedly atrophic but others are hypertrophic and congested. Complete obliteration of the capsular space by an overgrowth of Bowman's epithelium is fairly common as is also cystic dilatation of this space. Hemorrhages are not found either in the glomerular tufts of capsular spaces nor is hyaline droplet degeneration present in the capillary walls.

In the van Gieson's preparations there is seen a very extensive interstitial connective tissue increase everywhere in the cortex. In the scar tissue are moderate numbers of lymphocytes, both diffuse and in collections.

The pigment in regenerated cells and tubules contains no iron.

*Liver.*—Well marked fatty degenerative infiltration throughout the lobules.

*Lung.*—Unresolved organizing lobular pneumonia, purulent bronchitis.

*Rabbit BXI-B.*

Two cubic centimeters of 5 per cent lithium carmine injected intravenously 48, 24, and 3 hours before last administration of uranium. An additional cubic centimeter of carmine was given 24 hours after the dose of uranium. Killed 3 days after giving uranium.

*Autopsy.*—Weight 1670 gms. Skin, conjunctivae, mucous membranes, and skeletal musculature stained pinkish with carmine. No edema or free fluid in peritoneal or pleural cavities. Bladder contains 6 c. c. of carmine red urine. Left epididymis contains numerous small abscesses. Gall bladder is filled with glairy mucus.

*Kidneys.*—Combined weight 18 grams. Capsules not adherent, sur-

faces only slightly irregular and deep reddish brown. On section the parenchyma appears deep reddish and the normal markings are quite distinct on account of the alternate deep carmine red and pale streaks. Fine scarring is visible at the border of the cortex and medulla.

impregnation which occurs only in the first segment. Most of these cells are uninjured although an occasional one is found in which the nucleus stains red, a sign of cell death. Just beneath the capsule are numerous tubules filled with faintly carmine stained cellular debris. The carmine staining and close

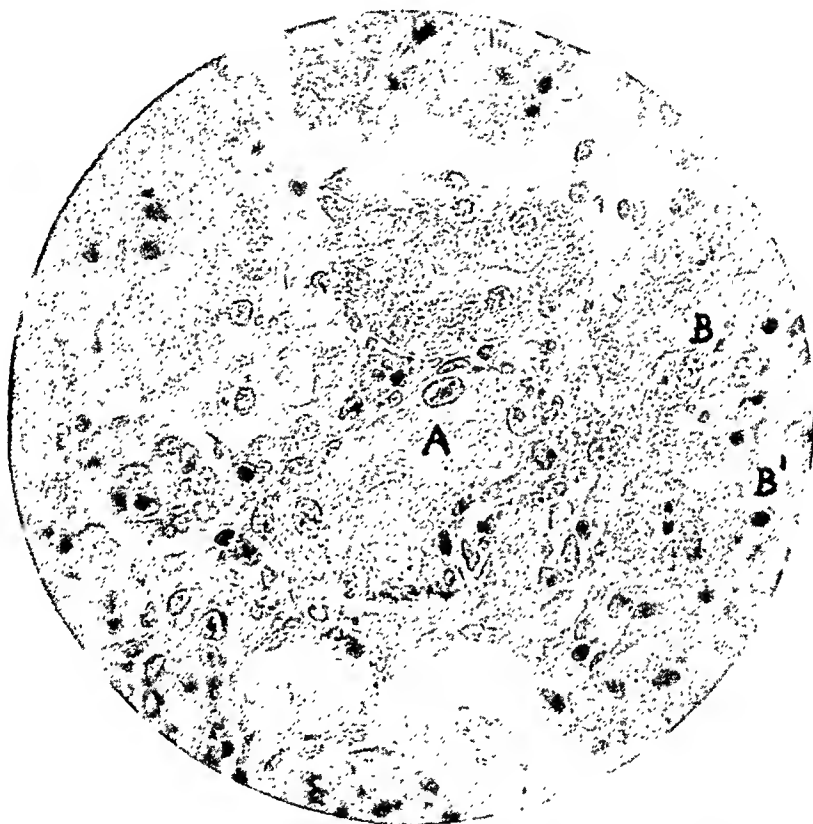


FIG. 9.—Rabbit BXI-B. Oil immersion. 'A' is a tubule lined by regenerated epithelium in the lumen of which there is carmine-stained detritus, indicating that the tubule is patent. At B and B<sup>1</sup> are two segments in which the original epithelium is undergoing necrosis. The final dose of uranium given three days previously was fifty-four times that known to kill original epithelium, yet there is no evidence of damage to the new cells.

*Microscopic.*—Intravital preparations show in all zones of the cortex one to three cross sections of proximal convoluted tubules with original epithelium located about the glomeruli, readily recognized because they are the only tubules which have taken up the carmine. Closer study reveals the heavy

proximity to the first segments indicates that these are second divisions of proximal convoluted tubules damaged by the last dose of uranium. No original epithelium of the third and fourth segments remains. Tubules with typical-appearing uninjured regenerated epithelium are found in the regions

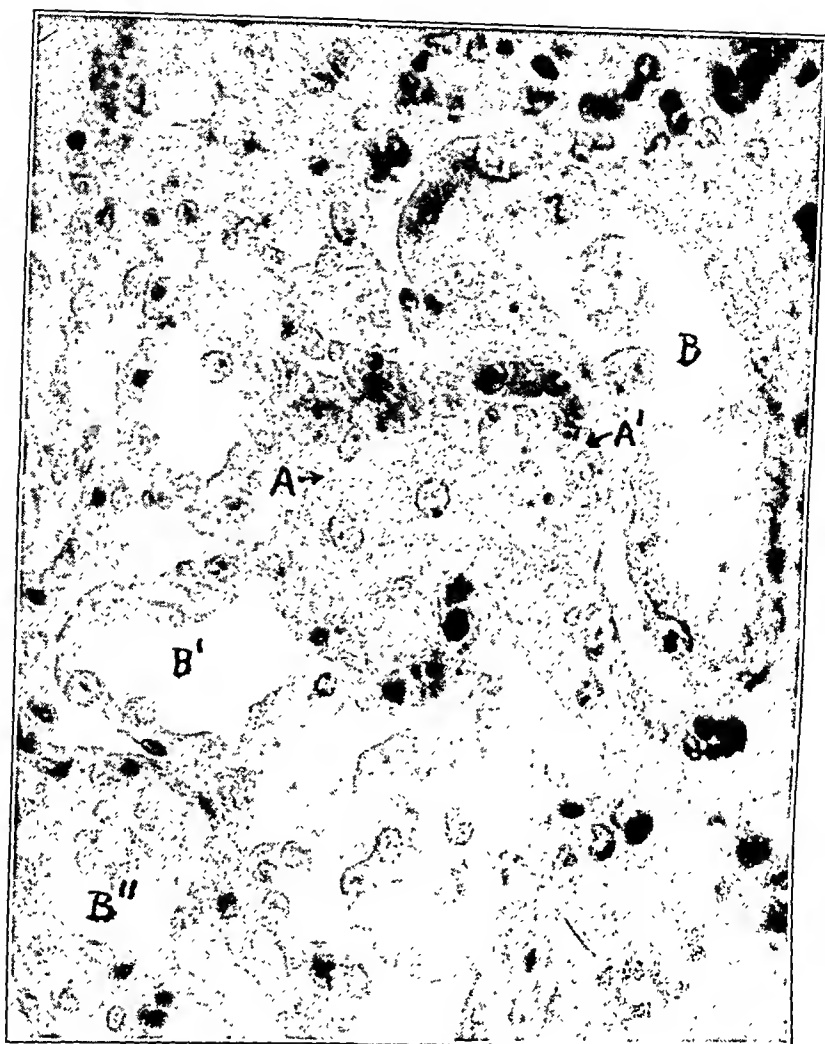


FIG. 10.—Rabbit 4-A. Oil immersion. A and A<sup>1</sup> are parts of a proximal convoluted tubule in which there is necrosis of the original cells, while in B, B<sup>1</sup> and B<sup>11</sup> the regenerated cell linings exhibit no evidence of injury. The patency of the latter tubules is evidenced by the presence of cellular detritus and well preserved red blood cells within their lumina. The last amount of uranium administered two days before was ninety-six times the initial dose.

just described and these cells fail to stain with carmine. That many of these tubules are patent is shown by the presence within their lumina of carmine colored dead cells or cellular detritus. Casts stained with carmine are also numerous in the limbs of Henle's loop and the smaller collecting tubules, further proving the patency of the regenerated tubules since in no other way could the carmine reach the

collecting tubules. Carmine is not found in any tubular epithelium except as above described. In some connective tissue cells and leukocytes there is a considerable amount of the stain. A few carmine emboli occur in the glomerular vessels but most of the stain here is within polymorphonuclear leukocytes.

In hematoxylin and eosin preparations there is no evidence of necrosis

in any of the new epithelium. Granular yellowish-brown pigment is abundant in the cytoplasm of many of these cells but is negative for iron.

The glomeruli present the usual picture of chronic uranium nephritis although atrophy is not extreme and cystic dilatation is not marked. Hyaline droplet degeneration of the capillary walls is absent. There is the usual

*Epididymis.* — Subacute purulent epididymitis.

#### DISCUSSION OF RESULTS.

The pathologic-histological alterations in the kidneys described are typical of all included in the immune series, varying only in degree. With regard to the condition of the regenerated epithelium and functioning glomeruli

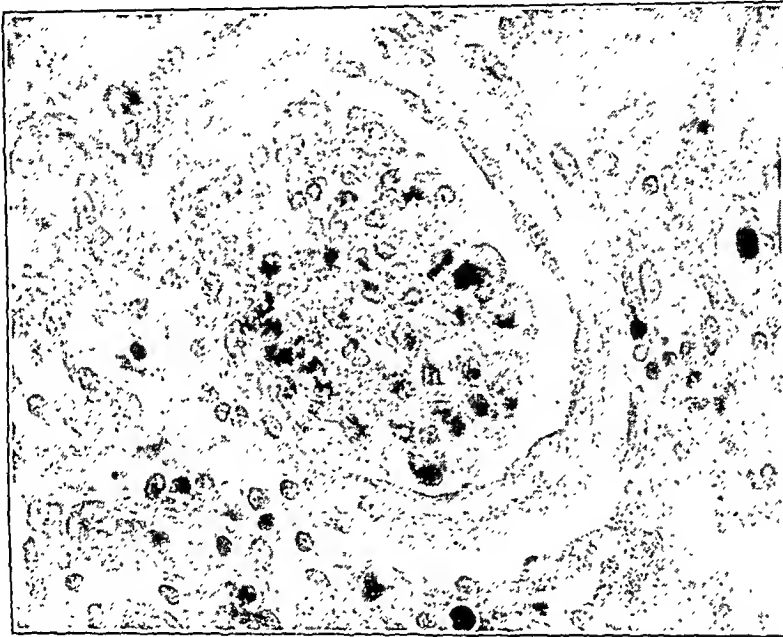


FIG. 11.—Rabbit 4-A. Oil immersion. Thickening and hyalin degeneration of membrana propria about glomerulus. Slight increase in number of cells of Bowman's membrane. Atrophy of glomerulus.

proliferation of Bowman's epithelium with the formation of an occasional crescent or obliteration of the capsular space.

Sections stained with van Gieson's mixture show the same changes described in other cases.

*Liver.*—Carmines is deposited in the reticulo-endothelial and stellate cells. No fat.

*Gall Bladder.*—Chronic catarrhal cholecystitis.

there is absolute agreement in all; in none is there any appreciable damage to these structures while in every one there is demonstrable injury to the original proximal convoluted tubular cells.

Experiments on non-immunized rabbits show that 0.001 gm. of uranium subcutaneously and 0.005 gm. intravenously is sufficient to produce cell death in the distal and transitional divisions of proximal convoluted tub-

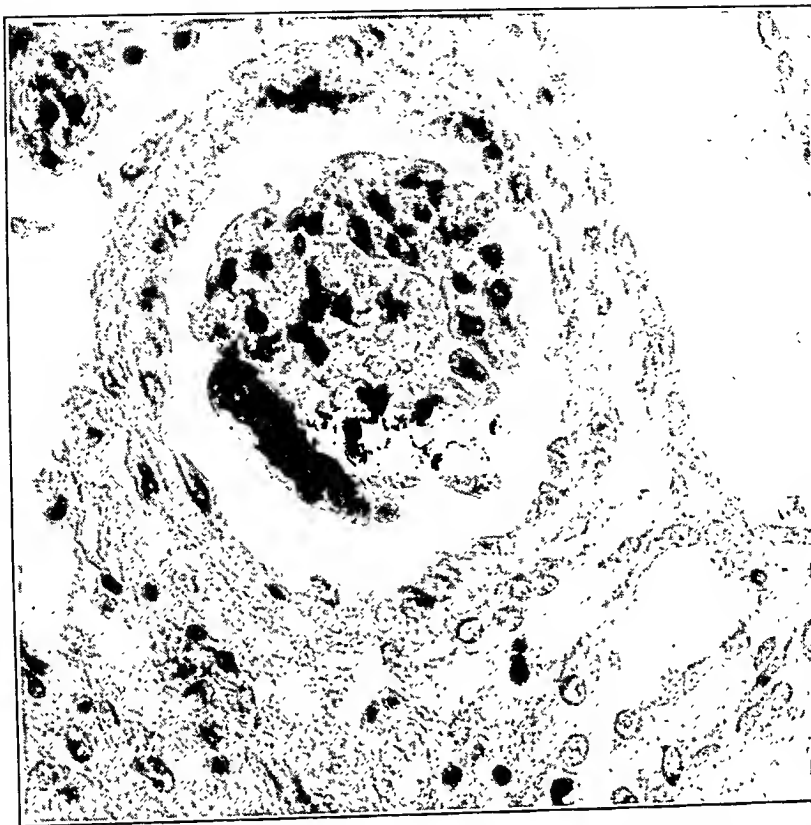


FIG. 12.—Rabbit 4-A. Oil immersion. Well marked hyperplasia of epithelium of Bowman's membrane. The glomerular capillaries contain a fair amount of blood.

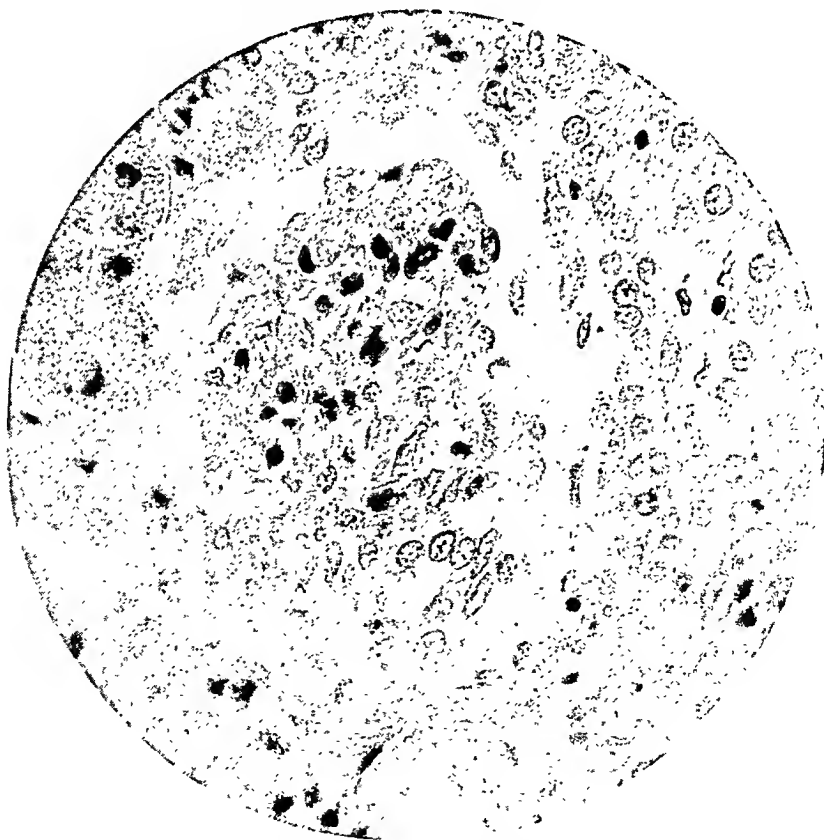


FIG. 13.—Rabbit BQI-B. Oil immersion photomicrograph showing a large epithelial crescent. Some capillaries in the tuft are well filled with blood.

ules and definite evidences of injury in the glomeruli. In immune series A, 64 to 96 times, and in Series B, 54 to 96 times, these amounts were administered without damaging the regenerated cells or the glomeruli.

found in the glomerular capillaries, the persisting epithelium of proximal convoluted tubules, dead epithelium in the lumina of some regenerated tubules, limbs of Henle and collecting tubules. Regenerated epithelium does

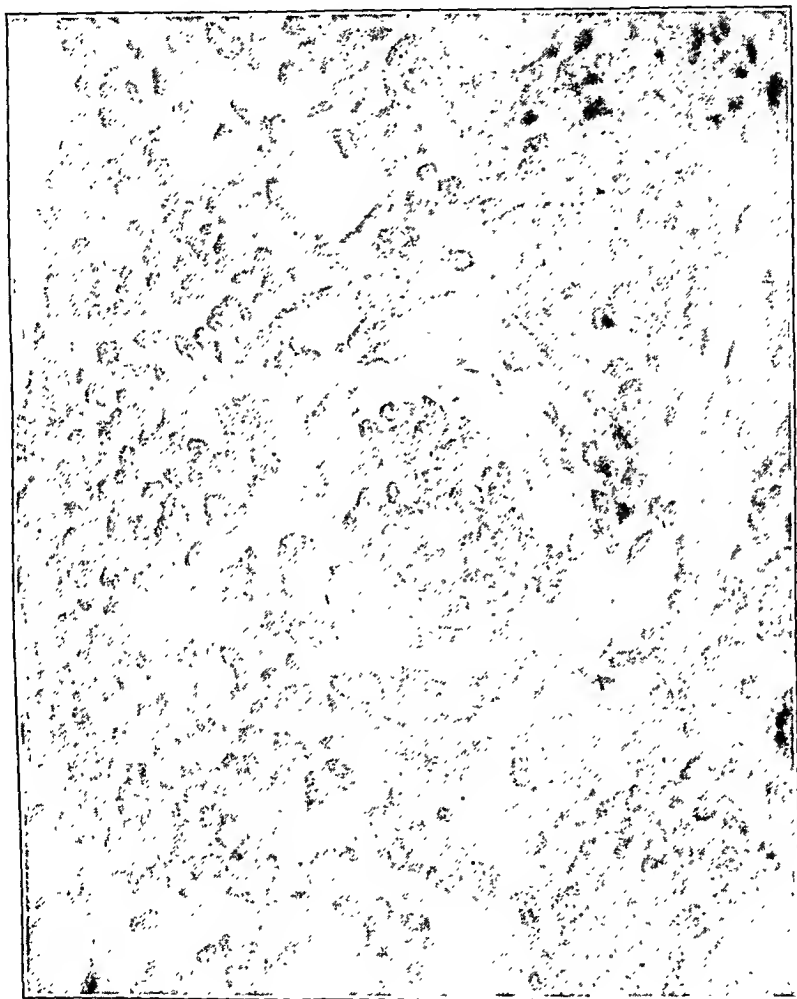


FIG. 14.—Rabbit BGI-B. High power. Obliteration of capsular space resulting from overgrowth of Bowman's epithelium. Marked glomerular atrophy. Numerous lymphocytes in the interstitial tissue.

That many glomeruli and regenerated tubules are patent in the chronic uranium kidney is demonstrated by the microscopic findings in three animals intravitaly stained with carmine (BLI, BTI, BXI). In all the stain was

not stain with carmine and for this reason any cells stained with the dye and found in the tubules must originate from some point nearer the glomerulus. Furthermore the carmine in Henle's loops and collecting tubules

could reach these only after having passed through the proximal convoluted tubular units. It is not unreasonable to suppose that if carmine is able to reach the various structures mentioned uranium might do likewise. Necrosis of the original convoluted tubular cells is of the type produced by

slowly. From the tables it will be seen that after the first two or three injections the rabbits frequently gained in weight and often weighed several hundred grams more at the end of the experiment than at the beginning. After the first few injections it was uncommon for the animals to refuse food for



FIG. 15.—Rabbit BGI-B. Low power photomicrograph showing a portion of a labyrinth well illustrating the pathologic changes constantly seen in the chronic uranium kidney. Very few proximal convoluted tubules with original epithelium remain; most of the tubules are lined by new epithelial cells. Some glomeruli are atrophic, others are hypertrophic. Pronounced increase in interstitial tissue.

uranium and there is no reason to believe that some of the poison did not come in contact with the regenerated tubules containing carmine stained detritus, yet in these there is no evidence of injury.

The highest percentage of immunization was obtained in Series A and B in which the dosage was increased

more than the first day or two and many exhibited no symptoms whatever.

The attempt to carry out Gil y Gil's procedure in his rabbit J.23 met with complete failure. Only one rabbit survived the initial dose of 0.002 gm. and this one died when the next dose of 0.008 gm. was given. But little better success was obtained with the tech-

nique employed in his J.24. Six rabbits succumbed after the second injection (0.008 gm.) and three more following the increase from 0.03 to 0.08 gm. and of these two were over the

fore any appreciable degree of immunity is attained.

Increasing the dosage by multiples of three proved unsatisfactory in the subcutaneous series because all ani-



FIG. 16.—Low power photomicrograph of entire kidney cortex of a mouse injected subcutaneously with 2 c. c. of urine from Rabbit 4-A on the second day after the rabbit had been given 0.064 gm. of uranium. The proximal convoluted tubules nearest the medulla show extensive necrosis of epithelium which has desquamated into the lumina. The type of the lesion and its location is identical with that of acute uranium nephritis in rabbits.

4-5 day limit and could not be included in the immune series because of regeneration having begun. Only one rabbit survived the entire series of doses. Such a rapid increase in dosage is unwise because most animals die be-

fore any appreciable degree of immunity is attained. Increasing the dosage by multiples of three proved unsatisfactory in the subcutaneous series because all animals died after the increase from 0.027 to 0.081 gms. and unfortunately after the beginning formation of new cells which necessitated excluding them from the immunized series. In the parallel intravenous group the results



would have been equally unsatisfactory had not the animals been killed before regeneration in the involved tubules began.

The results show that with uranium it is not possible to immunize the whole organism but a certain degree of tolerance is attainable. In series "A" this ranges from 16 to 40, and in series "B" from 9 to 40 times the lethal dose.

In my hands the colorimetric method used by Gil y Gil for the quantitative determination of uranium in the urine proved to be unreliable even when known amounts of uranium were added to normal rabbit urine. For some reason, perhaps due to pigments in the urine, such qualitative differences in color developed that accurate readings on the colorimeter were impossible. As has already been stated this method has very definite limitations because most specimens of urine from uranium rabbits contain blood. For these reasons I did not attempt to make colorimetric determinations in any of the immunized animals.

The biological method used by Gil y Gil proved reliable although it was found necessary to inject the urine subcutaneously rather than intraperitoneally since the latter procedure invariably killed the mice within a few minutes or hours. A number of mice were injected with 2 c. c. of sterilized urine from a normal rabbit, allowed to live four or five days, killed and the kidneys sectioned. No lesions were found, indicating that there is nothing in urine itself to injure the kidney. In order to study the localization of uranium in the mouse kidney several animals were given 0.0005 gm. dissolved in 2 ccs. of normal rabbit urine. After

four days typical but rather extensive necrosis was found in the proximal convoluted tubules.

To compare the excretion ability of an acutely poisoned kidney with that of a partially immunized one a rabbit was given a subcutaneous injection of 0.009 gm. of uranium and at the same time a like amount was injected in Rabbit 83-A which had had two previous doses (0.001 and 0.003 gm.). The urine from each animal was collected for three days following injection and 2 c. c. from each day's specimen administered to mice. The mice receiving urine from the first and second day's specimens of the non-immunized animal showed very slight epithelial damage but on the third day a moderate degree of necrosis was noted. Urine from Rabbit 83-A on the first day produced the same degree of nephritis seen in the acutely poisoned animal on the third day. A positive though slight nephritis was present in the mouse injected with the second day's specimen while that of the third day was negative. This would seem to indicate that even a partially immunized kidney is capable of excreting uranium more rapidly than an acutely poisoned kidney.

Rabbit BAI-B offers more definite proof of rapid excretion of uranium. The mouse given urine collected on the twenty-first day after 0.008 gm., had been given was negative. The rabbit was then given 0.016 gm. of uranium. Urine from the 4, 8, and 22-hour collections produced definite lesions in mice, very marked in the first and moderate in the others. Mice injected with urine from the third, fourth, and fifth days were negative. If we may

judge from the findings in other rabbits in the series dying at this stage, rabbit BAI-B must already have had a fairly well advanced chronic nephritis.

Rabbit 4-A was allowed a rest period of three months following the administration of 0.064 gm. thus offering the opportunity of determining how long an immunized animal would continue to excrete uranium in the urine. A mouse injected with urine from the twenty-first day after 0.032 gm. exhibited well marked uranium lesions. Urine from the first three days after giving 0.064 gm. contained enough uranium to produce extensive and widespread necrosis in the convoluted tubules. Following this the extent of necrosis gradually diminished but was constantly found up to the twenty-fifth day at which time daily injections of urine into mice were discontinued. Urine from the thirtieth and thirty-third days caused slight lesions but that of the thirty-fifth did not. Positive results were obtained with urine from the fortieth and forty-sixth days but were negative for the sixtieth and nintieth. In this rabbit also it is seen that while excretion occurred over a long period of time, the amount, as indicated by the intensity of the damage produced in mice, was much greater in the first three days than at any time thereafter.

This method was used in a number of rabbits besides those mentioned but the results are so similar to those of BAI-B and 4-A that repetition is unnecessary.

As a qualitative test for the presence of uranium in urine the biological method is reliable and apparently quite sensitive but it gives only a rough

indication of the quantity excreted. Judging by the extent of kidney damage in mice it would appear that the greater part of the uranium is excreted during the first three days after a given injection but with higher dosages in immunized animals small quantities may be excreted for a considerable length of time.

Potassium ferrocyanide was used as a qualitative test for the presence of uranium in all urines examined. The specimens were diluted with water to weaken the yellowish or brownish color of the urine, acidified with acetic acid and to this was added a few drops of 5 per cent potassium ferrocyanide. It is interesting to note in connection with biological results that a strongly positive test for uranyl ferrocyanide was obtained in the first twenty-four urine from rabbit 4-A after the administration of 0.064 gm. The test was negative in all subsequent specimens. After the injection of 0.08 gm. this animal passed no urine on the first day but the specimen obtained on the second day gave an unmistakably positive test for uranium. The test was weakly positive on the first day after the final dose of 0.096 gm. In rabbits 15, 80, and 81-GyG-J-24 strongly positive reactions for uranium were obtained in the urine passed on the first day after injection of 0.08 gm. but were negative thereafter.

A quantitative method for estimating uranium in body tissues and fluids which appeared to give accurate results in the hands of Karsner, Reimann, and Brooks (46) was next tried. Unfortunately there is some ambiguity in

(46) Karsner, H. T., Reimann, S. P., and Brooks, S. C. Studies of uranium

poisoning. II The solubility of uranium oxide in artificial and human gastric juice. *J. Med. Research*, 38: p. 163-168, 1918. *Ibid*, p. 169, III. The question of renal tissue affinity for uranium.

the outline of technical procedure and this led me into an error which was not discovered until too late to rectify. It was found on adding potassium ferrocyanide that iron was still present in the solution titrated. The results were therefore unreliable since iron also oxidizes potassium permanganate and the figures obtained were for both metals.

That considerable uranium was often present in the urine from a number of rabbits having the largest doses I am quite sure. In practicing the method, known quantities of uranium nitrate were added to urine and in the ash after incineration the yellow color of uranium oxide was always visible. In the urine from immunized rabbits this was likewise true in several instances.

The quantitative estimation of uranium excretion might well be made the basis of a separate study.

Schneider (47) working with uranium poisoned *Petromyzon fluviatilis*

(47) Schneider, G., *Ein Beitrag zur Physiologie der Niere niederer Wirbelthiere*, Skand. Arch. f. Physiol. 14: p. 383-389, 1903.

found that by using a fixing solution consisting of potassium ferrocyanide, picric acid and HCL, uranyl ferrocyanide was precipitated in the renal epithelium.

This method was tried in both acutely poisoned and immunized rabbits but without positive results. In the regenerated epithelium of two immunized

animals an abundance of yellowish-brown granules was found but the appearance is exactly the same in sections stained by ordinary methods so that it is very unlikely that the substance is uranium.

The nature of the pigment so constantly observed in regenerated epithelium is uncertain. It is non-iron containing and therefore cannot be hemosiderin. It may possibly be derived from bits of necrotic cell cytoplasm not infrequently observed in the process of being engulfed by the new epithelial elements although I have never observed an intermediate stage between the pink-staining masses and the yellowish-brown pigment.

If the liver is damaged by uranium one would expect some histological change in the cells and with this possibility in mind I have studied this organ routinely along with the kidney. In the acutely poisoned animals after small doses nothing was found. As the dosage in immunized animals was increased some constant and very striking changes were observed. In animals of series "A" dying or killed after the administration of 0.064 gm. of uranium a slight but definite fatty degenerative infiltration was noted. In one animals (6-A) living fourteen days after injection of 0.064 gm. this was very slight, possibly indicating that the change is transitory. All rabbits succumbing from the effects of 0.08 or 0.081 gm. had well marked fatty change diffusely in the lobules but still most marked toward the central veins. Those dying after 0.096 gm. exhibited extreme fatty degenerative infiltration involving the entire lobules with the exception of a thin rim of cells about

the portal veins. The liver in these animals grossly appeared yellowish, very friable and distinctly fatty.

In the intravenous series, with the exception of one animal in which a slight degree of fatty change occurred after giving 0.016 gm., fat was detected only after 0.032 gm. had been given. One rabbit which lived for 20 days after a dose of 0.032 gm. showed no fat in the liver. In rabbits given 0.04 or more grams the fatty degenerative infiltration was comparable in extent with 0.08 and 0.096 gm. in the subcutaneous series. In every instance specific fat stains were made to check the findings. Very little actual necrosis was visible in the hepatic cells and evidences of cellular regeneration were never found. The significance of these changes is debatable. Fatty changes are known to occur in the presence of many toxic and metabolic disturbances and it is possible that this alone is sufficient to account for the liver damage. The only certain way of settling the question is by quantitative estimation. This was attempted but the same difficulty of freeing from iron previously mentioned was encountered and the results were inconclusive.

Even if uranium is taken up by the liver the fact of immunity on the part of renal tubular epithelium is not disproven since it has been shown that even after the largest doses of uranium the kidney is still able to excrete the metal in sufficient quantity to give positive qualitative and biological tests.

After having demonstrated the fact of immunity it appeared desirable to determine whether this is transitory or more or less permanent.

Rabbit 4-A after receiving 0.064

gm. was allowed a three-months rest period after which the next regular increase in dosage, 0.08 gm. was administered. During the rest period the animal gained 450 gms. and was to all external appearances a healthy rabbit. Following 0.08 gm. the animal reacted fully as well as others allowed the usual three-week period between injections.

In series "B," rabbits BCI, BEI and BGI were chosen quite at random from others at the same stage of immunization and no further injections were given for nine weeks. During this interval all gained slightly in weight and appeared well and lively. At the end of the rest period all received 0.024 gm. Following this dose the animals were quite sick but survived and the doses were later increased in the regular manner. BGI in the end showed the greatest tolerance in the intravenous series.

The series is too small to draw definite conclusions as to the permanency of the immunity but so far as they go indicate that immunity is retained for an appreciable length of time.

#### SUMMARY.

Uranium nitrate produces in the rabbit a glomerulotubular nephritis which in the chronic stages resembles that seen in the human. It is true that tubular lesions are more prominent than glomerular in all stages of the disease but some alteration in the latter will be found in all instances.

Repair begins early in the epithelium of the tufts and Bowman's membrane. Frequently the number of new cells is excessive and leads to the formation of epithelial crescents and even complete obliteration of the capsular

space, glomerular atrophy and hyaline degeneration. In the chronic stage it is rare indeed not to find at least some proliferation of Bowman's epithelium. In other instances the capsular space is dilated and cystic with atrophy of the accompanying glomerulus. In even the most markedly scarred kidneys there are always some hypertrophic and apparently functioning glomeruli.

The same glomerular lesions Baehr (32) produced by intra-arterial injection of very small quantities may be brought about by repeated and increased doses administered either intravenously or subcutaneously.

The regenerative capacity of renal tubular epithelium after injury by uranium is remarkable, particularly when the doses are so graduated that not all cells are killed at one time and when sufficient time is allowed between injections for complete restoration.

#### PROOF OF IMMUNITY.

1. It has been shown by experiments on normal rabbits that 0.001 gm. of uranium administered subcutaneously or half this quantity intravenously, will produce unmistakable histological evidences of injury in the glomeruli and epithelium of the distal and transitional segments of the proximal convoluted tubules. In the glomeruli these changes are swelling and desquamation of epithelial cells, diapedesis or hemorrhage into the capsular space, intra-glomerular hemorrhages, and hyaline droplet degeneration while in the tubules there is complete necrosis of cells.

2. If subsequently larger quantities than are known to produce these lesions can be administered without evidence of damage it may fairly be

assumed that the glomeruli and regenerated tubules have acquired an immunity for the injurious agent, providing it can be proven that the poison still comes in contact with these structures.

3. That uranium still passes through the kidney with chronic injury is shown by the proximal convoluted tubule by necrosis of epithelium in segments of the proximal convoluted tubule which are not injured until large amounts of the metal are given.

4. Intravital staining of the chronic uranium kidney with carmine proves that many glomeruli and regenerated tubules are still functioning. It is unreasonable to suppose that uranium reaches the same structures as the distal tubule.

5. The biological and qualitative tests on the urine from immunized rabbits prove conclusively that the animals are capable of excreting uranium both rapidly and in considerable amounts.

6. Numerous rabbits have been given both subcutaneous and intravenous doses of uranium from 54 to 96 times greater than the quantity known to produce glomerular and tubular damage in a normal animal yet without evidence of injury being shown.

#### MECHANISM OF THE IMMUNITY.

Experiments with mice show that although sufficient uranium is excreted in the urine of rabbits on the first and second days of the acute stage to produce slight kidney lesions in mice it is not until the third day that enough is present to evoke much of a nephritis. The rate of excretion is in inverse proportion to that of partially or fully immunized animals. Why is little or no uranium excreted by the acutely damaged

aged kidney while the immunized organ permits its ready passage? The most plausible explanation lies in the action of the salts of heavy metals. It is well known that these salts, including uranium, precipitate proteins and form metallic salts of albumins (albuminates). Unless a very large quantity of uranium is administered it would appear that there is sufficient protein in the susceptible parts of the kidney apparatus to combine and fix the poison so that little or none will be excreted in the urine until the dead cells (uranium albuminate) become detached and washed out of the kidney. Microscopic examination of the kidney and urine shows that after two or three days many cells in the renal tubules have already been fused into casts and will also be found in the urine. This would explain the appearance of the more marked nephritis in mice given urine on the third day after injection of a non-immunized rabbit.

In the immunized kidney on the other hand little original epithelium remains in the susceptible parts of the tubules. By gradually increasing the doses of uranium the greater part of the original epithelium has been destroyed and replaced by vastly different appearing cells in which no histological evidence of injury is to be

found. Such kidneys in contrast to acutely poisoned organs allow uranium in appreciable quantities to pass through into the urine.

Two possible explanations for the failure of the poison to injure the regenerated cells are offered: (1) The chronic uranium kidney is unable to excrete uranium, (2) the regenerated epithelium has acquired an immunity for the poison.

The first is readily disposed of since it has already been shown that uranium is excreted.

The most logical explanation of the mechanism of the immunity is to assume that the regenerated epithelium is able to prevent the poison from uniting with the cell protein. In this event it would be expected that the injurious substance would be excreted in the urine, and such is the case. Another possible explanation is that the new cells are capable of taking up the poison and detoxicating it, but the amount excreted in the urine and the failure to find the metal in the epithelium by the use of a specific fixative makes this improbable.

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# Heart Strain and Its Consequences\*

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THE subject of mechanical strain of the heart and great vessels has been considered in its clinical aspects in the medical literature since the middle of the nineteenth century. Following the pioneer work of Peacock, da Costa, Traube, Seitz, and Allbutt and Roy, the condition became recognized as a clinical entity. To Allbutt the greatest credit is, perhaps, due for describing a large number of cases, clearly demonstrating the operation of overwork and stress in the production of cardiac diseases—factors that had previously been overlooked or neglected by pathologists. The opportunities afforded in modern industry for the study of this subject have still further elaborated our conceptions of heart strain, at the same time verifying the opinions held by the great clinicians.

Of recent years, the subject has assumed increasing importance. The advent of compensation laws in England, Germany and the United States has been a great stimulus to the analysis of the medical aspects of this subject. The broad and considerate interpretation of the law, especially by the English courts, has redefined the terms "accident" and "injury," "disability" and "compensation," so that whatever injurious happens to an in-

dividual during work must be considered in its relation to the occupation.

The effect of strain upon the heart is now beginning to receive a revived interest also, since our attention has been focussed, during the past decade, upon the increasing prevalence and economic significance of heart disease in general.

## DEFINITION

Heart strain is an organic condition associated with the sudden development of symptoms, referable to the heart and aorta, which can be attributed to some unusual muscular effort or overexertion, and which results in physical disability of varying degree and duration. The emphasis is placed upon the subjective complaints of the patient, because they are the outstanding features which bring the condition to our notice. It is the sequence of cardiac symptoms following effort that gives the clinical picture its individual character.

## ETIOLOGY

*Strain of the Healthy Heart.*—Like disease, health is also a relative term. In harmony with the liberal interpre-

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tation of the compensation laws, we must assume for practical purposes that strain of the healthy heart is possible. This implies the acceptance of the generalization that the heart is healthy, from a labor standpoint, if a man is able for a long period to pursue his strenuous occupation without distress and without long periods of absence from work.

It must be emphasized that, regarding the safety of the heart, physical training, which has its beneficial effects upon the circulation, is of the first importance as a preventive against cardiac strain. A person properly trained in the laborious manoeuvres of his occupation and the postural leverage to be used need not fear cardiac strain as much as one unaccustomed to the labor.

Athletes who make violent efforts for shorter or longer periods allow plenty of time for the heart to recover in the intervals. However, the observations made in athletes indicate that prolonged overexertion, even in the trained individual, may affect the heart. Feats of strength and endurance cannot fail, sooner or later, to leave their marks upon the respiratory and circulatory systems. Among the most notable causes of strain in athletes are rowing, running, and fast bicycle riding. Thus, in one Marathon race, the leading runner collapsed in the last quarter-mile with an extremely enlarged heart as a result of the exertion. The hearts were also dilated in the second and third winners in the same race. An English Rugby International suddenly collapsed during a match. So also did a young professional football player at the begin-

ning of the season after vigorous exertion in the practice games. His heart was dilated or hypertrophied to five inches to the left of the midline of the sternum before the game in which he broke down. In some circumstances, a single feat of violent exertion may be followed not only by prolonged, or even permanent, inability to take exercise, but also by pathological dilatation of the heart or other signs of myocardial defect.

Heart strain may therefore be fully explained as being the outcome of extreme or prolonged exertion, with resulting diminished contractile power. It will come on earlier when there has been some pre-existing abnormal condition, such as increased blood pressure, or when the heart is not mature—as in young adolescents who do too vigorous exercise.

*Occupation.*—As long as human effort is utilized to drag, lift, pull, or push weights that should be relegated to mechanical apparatus, there will inevitably be disastrous effects upon the human organism in consequence of strain. This applies to all occupations where effort of this nature is demanded. With the changing conditions and enlightenment in the industries, it will apply more to some occupations than to others. It will take its human toll inevitably until it becomes recognized that the power of muscles in the human machine must not be stressed to the extreme. There is an exacting compulsion of labor in industry without sufficient regard to the conservation of the energy of the individual, especially in certain occupations. Thus forgemmen, rivetters, hodmen, stone masons, sailors, soldiers,



longshoremen, blacksmiths, porters, metal workers, and miners are still compelled to exert great and often sudden and violent effort while at work.

The part of stress in the causation even of chronic cardio-arterial diseases comes out plainly when such cases are considered in numbers large enough. When, for instance, large numbers of persons engaged in laborious callings are contrasted with large numbers of those whose pursuits are mechanically less urgent, a predominating excess of cardiovascular involvement in the laborers is found. As an occupational effect, therefore, chronic cardiac disease is most frequent among these classes of workers.

In the production of acute or primary cardiac strain, however, the occupation of the individual is not of material importance. The heart of a man engaged in strenuous labor is enabled by adjustment to support rather severe physical exertion. Similar, or even milder sudden exertion in a man unaccustomed to it, is likely to produce heart strain.

Of fifteen cases of primary heart strain recently examined by us, the occupations were given as follows: Laborers 4; helpers on truck 2; mechanic's helper 1; mechanic on wind organs 1; porter 1; shipping clerk 1; iron worker 1; electrical worker 1; plumber's laborer 1; janitor 1; driver 1.

For years a man may pursue a laborious occupation without any apparent ill effects. But on one particular occasion, such as lifting a heavy case in an uncomfortable or unusual posture, acute heart strain will develop. It is impossible, of course, in such

cases to evaluate the predisposing effects of the continual duress of labor. The condition of acute primary strain must always be considered an accidental occurrence, and stress of occupation must be accepted simply as a predisposing etiological factor.

*Chronic Infections and Intoxications.*—Attacks of an infection, manifestly or insidiously, often so impair the cardiac muscle and so reduce its resiliency as to render it liable to yield prematurely or unexpectedly to overwork, with consequent strain. Chronic stress is so intimately confused with toxic factors, that it is often exceedingly difficult or even impossible to distribute its due weight to each of these several causes.

Chronic alcoholism, tobacco, and venereal disease, are unquestionably very important contributory causes of heart strain. They produce effects, usually of a degenerative nature upon the heart muscle.

The dilatation of the heart in severe and prolonged anemia, as well as that which occurs after acute illness, must also be considered a form of heart strain. Other factors, sheer fatigue, infections more or less latent, sudden emotion or prolonged grief, insufficiency of sleep, the worries of lessons, puberty, inherited nervousness, excess of venery, and other such incidents also predispose to strain.

Exercise, therefore, though not severe enough to be injurious to a healthy heart, may actually strain a heart whose nutritive condition has become less than normal.

*Previously Existing Heart Disease.*—Unusual exertion may reveal a lat-

ent defect in a heart which under ordinary circumstances, or for some time at any rate, would have passed as sound. In men of middle age, a breakdown of the heart is often thus acutely determined; but in later life it is usually very difficult to distinguish between lesions due mainly to variations of stress and resistance, and those due to the tooth of time.

Pre-existing heart disease is often discovered at the time complaint is made of the symptoms developing during work. The forms of heart disease thus discovered usually fall into the classical valvular and myocardial conditions, presenting the typical signs. Upon close questioning and careful investigation, there may also be discovered the usual etiological factor of a previous acute infection. Tonsillitis and rheumatism are particularly conspicuous among the causes, and often a history of tonsillectomy or a stay in a hospital for rheumatic infection is part of the past history. Given these previously existing heart conditions, we must eliminate those signs which can be attributed to them, before considering the superimposed effects of any strain upon the heart. Overexertion will, however, at times produce precordial pain which previously was not felt to any marked degree in a heart already diseased, and may induce changes in the heart rate as well as initiate disturbances which lead directly to cardiac failure. In these cases, therefore, the question of aggravation of a previously existent heart condition must be considered.

*Age.*—In patients over forty years of age, it is usual to find a degree of substitution of fibrous for elastic tis-

sue in the aorta with consequently lessened elasticity of the wall. If this is exceeded by some unusual exertion in lifting or pulling, the resulting strain on the aorta and heart may be irreparable. It is in this period of life that the aorta and ventricle are especially liable to permanent injury due to strain.

*Sex.*—It is natural to expect males rather than females to develop heart strain in industries, because of the greater liability of the former to sudden physical exertion. Cases of heart strain and consequent cardiac pain in women who have undertaken sudden physical stress in their homes, however, are known. A case of rupture of the aorta in a healthy woman has been recorded during the pains of labor and childbirth.

*Exciting Cause of Heart Strain.*—Excessive exertion such as is entailed in sudden lifting, pulling, pushing, straining, stair or mountain climbing, especially supporting a load, etc. is the only exciting factor in the production of acute primary heart strain.

To illustrate from our series of cases the uniform importance of the exciting cause of heart strain, the patients' statements are given:

During severe straining in a difficult and uncomfortable posture to push up a case weighing 100-120 lb., suddenly became unconscious, and on awakening had severe pain in the heart.

While lifting the end of an iron railing weighing about 1500 lb., suddenly felt a severe sharp shooting pain from the right upper abdomen up to the left pectoral region.

While lifting a transformer weighing about 150 lbs., felt a sudden sharp knife-like pain from the shoulder down to the costal margin.

While carrying a bag of sugar weighing 100 lbs. up one flight of stairs, felt a tearing pain in the region below the left breast.

While supporting and carrying an iron pipe 40 inches in diameter and 29 feet long, felt slight pain and soreness from the left shoulder down to below the breast.

While pulling a very heavy organ, was suddenly seized by a very severe sharp pain in the left breast region. While lifting a very heavy stone, felt as if something were tearing in the lower sternal region.

While lifting an ice box, felt sudden sharp knife-like pain in the left lower chest.

During a fire, tried to pull apart the iron bars across the windows of the room in which he was trapped, and following the accident was extremely dyspneic with sticking pain in the region of the heart.

#### MECHANICS OF THE CIRCULATION IN HEART STRAIN

Although the machinery of the circulation allows for a rather wide field of responsiveness to effort, there are definite limits beyond which any attempt on the part of the heart and aorta to maintain adequate circulation is organically injurious to these tissues. The normal heart naturally adapts itself to those stresses which, in various degrees, all have to encounter. We must, however, be able to recognize the signs of any overstep-

ping of the normal limits of the heart's responsiveness.

The various effects of stress upon the heart may be considered with regard to the amount of the stress, the frequency of repetition or intermittence of the stress, the time allowed for rest and recovery, and the previous training of the heart to receive the stress to which it is exposed. These aspects are particularly apposite when practically considered from an industrial standpoint.

It is mainly in the laborious industries that strain affects persons of otherwise healthy body. By a single or persistent muscular effort the organs of the circulation may be urged to a menacing or hurtful degree. Efforts of less severity may tell upon a vascular system already somewhat impaired by other causes. Thus, if we assume a trained man to be working continuously with his muscles at a uniform but moderate rate, the total daily blood pressure in his arteries would not be above the mean of that of people in light occupations. If we assume the same man to carry a load up a flight of steps every ten minutes—although still the mean of his blood pressures and cardiac output for 24 hours may not be excessive, the maximum pressure, that is, the initial rise at the outset of each effort, may be very high.

Again, if we take another man, one who does not carry loads hour by hour and day by day, but who takes a load up occasionally—in him the maximal arterial pressure, as he shoulders the load will be driven much higher than under the same effort more regularly undertaken by, for example, a porter whose thoracic capacity, blood volume,

and vascular distributions are accustomed to such recurrent stresses. And if a clerk or one in a sedentary occupation were to shoulder a load, his defect in the automatic adaptations to such exercise might cause so sudden and relatively so great an increase of arterial pressure as to embarrass, to dilate, and even to strain his heart; possibly indeed to rupture some part of it.

"Tone" is used to express the amount of energy which heart muscle fibres can develop during systole. Since stretching in a rather wide measure increases the contractile power or tone of the heart muscle fibres, the heart under stress dilates. With further dilatation, as in fatigue, the tone lessens. The muscle fibres completely recover, however, without any persisting organic change.

With heart strain, there occurs an actual stretching of the muscle fibres beyond the limits of their elasticity. Strain, then implies a permanent change in the intracellular and interfibrillar structure. The loss of tone in heart strain is due to an organic change and complete recovery is impossible. If the heart after strain cannot maintain the output necessary during rest, it dilates gradually, and under its steady pressure the pericardium also will give way and the condition becomes irremediable.

It appears probable then that the principles which underlie the working of the normal heart also hold good for the behavior of the heart during over-stress. As long as the fibres of the heart or aorta have not been mechanically stretched beyond the limits of

their elasticity, heart strain cannot be said to have occurred.

#### PATHOLOGY

Heart strain, from a pathological standpoint, is the effect of stress or reiterated stresses upon heart muscle with resultant stretching of the fibres beyond their elastic limits. The occurrence of the particulate alteration in muscle fibres as a result of mechanical stress is obviously very difficult either to prove or to disprove pathologically. But the pathological dilatation of the heart which may occur, clearly implies the existence of some structural change in the heart muscle, which interferes with the normal transformations of energy, of which visible contraction is the outward sign. The suggestion that strain of the muscle fibres, by permanently altering their elastic state, allows the heart passively to dilate to excess, appears to provide an adequate explanation of the dilatation; and at the same time places it in the category of pathological rather than physiological dilatation.

It is relatively seldom that pathological examination of the heart can be made promptly after it has endured acute strain. The opportunity arises when the strain has caused prompt supervening death. In such cases, there is found partial or complete rupture of the heart or aorta at the site of pre-existing aneurysm or extensive degeneration in either location.

Postmortem pathological findings in a case that has shown symptoms of heart strain some years before death cannot be adjudicated with any precision to the various factors involved in producing the lesions found. However, certain morbid processes are at-

tributable to previously existing diseases; others, particularly in the vessels, to previous deterioration as a result of chronic stress; while still other lesions may be considered, by exclusion, the result of the acute strain under our consideration.

Pathological lesions in the heart and aorta which have undergone strain can therefore be classified as follows:

1. Previously existing cardiovascular lesions due to antecedent acute or chronic infections, intoxications, and senescence.

2. Gradual deterioration of the vascular system due to hard muscular labor during long terms of years, especially in middle age.

3. Disease of the aortic area and valves produced by sudden stress or extraordinary effort—the result of acute heart strain.

4. Injury to the heart muscle resulting from the same cause.

This classification distinguishes acute strains from chronic; the effect, that is, of some instant or brief stress upon the heart from the deferred effects of protracted labors. It also distinguishes injuries of the valves from those which in the first instance affect the walls of the heart.

*Diseases of the Aortic Area of the Heart*—Syphilis, anemia, chronic alcoholism, gout, lead poisoning, as well as the processes and products of senescence are conducive to the degenerative changes which invade the aortic region of the heart. Connective tissue fibre, when substituted for muscular fibre, as we find commonly in old hearts, gives to the part a higher resistance but at the cost of resilience;

so that once overstressed this fibre never recovers its former condition.

*Hypertrophy*—Hypertrophy of the left ventricle is a consequence of exertion in consonance with the recognized compensatory capacity of muscular structures in the body. It is to be regarded simply as the static expression of increased function, or of a larger contraction volume. This hypertrophy may be transitory or more or less permanent. In either case it produces an effect on the associated parts. The line between the aortic area of the heart and the aorta itself being no barrier to the extension of disease, the aorta dilates; its elasticity is impaired; its walls are diseased; and the coronary arteries become themselves less pervious or are blocked at their orifices.

*Coronary Disease*—A grave feature of atheromatous degeneration is that these changes involve, sooner or later, the orifices of the coronary arteries. From the first, perhaps, these arteries, like the rest of the aortic area, suffer under excessive percussion and the extreme variations of pressure. A hypertrophied ventricle, which is usually present in these cases, may at first be able to supply the increased nutrition which its greater work demands. With coronary involvement, however, the heart will receive by this route considerably less than its normal nourishment.

Notwithstanding this deprivation, the hypertrophied muscle sometimes retains a fair degree of functional value in a person of comparative inactivity. This is probably explained by the very slow progress of the lesion

allowing for re-adaptation of the heart.

*Cardiac Dilatation*—Dilatation of the heart is due to continuously excessive aortic pressure. Allbutt indicates that there are three modes of dilatation: active adaptive physiological dilatation to receive large volumes of blood; passive but remediable dilatation with abatement of tone or more gradual fatigue; and the irremediable atonic dilatation due to acute primary heart strain.

When the ventricle opens to receive the larger loads of blood there need not be any loss of tone. The cavity, by some vital endowment enlarges to receive the excessive quantum without any rise of intraventricular pressure. This is what occurs in chronic valvular lesions. In disease, as compared with experiment, we have the important factor of time and of changes gradual enough to allow of re-adaptation. When in acute strain, tone of some fibres begins to fail atonic dilatation supervenes.

In cases of death following acute strain, the cavities of the heart are usually dilated and the muscular walls frequently show a certain amount of antecedent hypertrophy with or without degeneration.

*Rupture of the Aortic Valve*—It is well known that sudden effort is capable of producing rupture of the aortic semilunar cusps. In the old experiments of Potain on the cadaver, a pressure of 300 mm. of mercury in the aorta was shown to be injurious to the aortic valves. Marey found that the intrathoracic pressure after effort often rose to this height in the large arterial trunks. The sudden increase

of pressure following effort in individuals whose usual level of pressure is already high is even more marked, and such individuals are more likely to suffer aortic valvular rupture.

Aortic insufficiency due to muscular strain is divisible into three classes: a few cases of sudden rupture of a healthy valve and sound aorta; cases of sudden rupture of a valve previously impaired by some local lesion or general disease; and cases of insidious forcing of the valve by the importunity of repeated muscular stress, probably with valvulitis.

It must be reasoned that if a certain amount of effort can be the exciting cause in producing acute heart strain in a predisposed heart, a greater stress may produce a lesion in an anatomically intact heart. Thus muscular exertion, very sudden or excessive, and attended perhaps by fixation of the chest walls with arrest of breathing, may produce direct rupture of a cusp of the aortic valve. The occurrence is not necessarily occupational. We recently observed its development following an effort to swim made by a plethoric man of 50, with hypertension.

One or more of the cusps may be torn; the posterior cusp is said to be the most frequently injured. A cusp may split from the free border across, or it may be torn at the base from its attachment. In one case an aortic cusp was forced inwards, and a pouch driven out from the wall of the aorta above it.

*Rupture of the Aorta or Heart*—The possibility of rupture of a healthy aorta under strain is mooted academically, though a good many reported cases seem to answer this question in

the affirmative. In general, the age incidence of spontaneous rupture of the aorta is widespread, indicating no uniform etiological factor. Thus, in a patient of Allbutt's, a very healthy boy aged 13, rupture of the aorta took place a little above one of the cusps of the valve during very severe exertion. In several cases, there was found very little pre-existing disease in the region of the rupture, while in a larger number there were present unmistakable signs of luetic or arteriosclerotic disease, or pre-existing dissecting aneurysm. In all cases, the sudden increase of blood pressure during work was the exciting cause in producing the rupture.

From experiments on animals it seems that on suddenly produced insufficiency of the aortic valve, the aortic pressure may be so great as even to rupture the unprepared ventricle. In one such case reported, there occurred also sudden rupture of the posterior pillar of the lower mitral cusp. It is almost certain, as was maintained by Morgagni, that a rupture never occurs in a sound heart muscle.

In the etiology of rupture of the heart, coronary sclerosis holds a pre-eminent place. In consequence there develops ischemic necrosis with thinning and replacement fibrosis and the formation of aneurysm of the left ventricle due to the high intraventricular pressure. Fatty infiltration of the heart muscle or brown atrophy due to the slow coronary sclerosis of age may exist. In all these cases, the sudden increase of blood pressure during work plays a critical role in precipitating the rupture of the heart.

The pathological conditions found may be tabulated as the chronic effects of prolonged stress and the effects of acute strain as follows:

#### I. Effects of Chronic Stress

1. Atheroma of the aorta and arteriosclerosis
2. Hypertrophy of the heart
3. Cardiac dilatation
4. Coronary artery disease
5. Aneurysm of the left ventricle
6. Aneurysm of the aorta
7. Temporary diminution of tone or contractile power of the heart, as after fatigue.

#### II. Effects of Acute Heart Strain.

1. Stretching of fibres beyond their elasticity, or dissarrangement of organic relation between fibres.
2. Tearing of fibres in the aorta or the heart wall.
3. Rupture of aortic semilunar cusp
4. Rupture of aorta or aortic aneurysm
5. Rupture of the heart or an aneurysm of the ventricle.

#### SYMPTOMS OF ACUTE HEART STRAIN

*Onset*—Characteristically, the symptoms of acute heart strain arise during or almost immediately after the performance of some strenuous work. The organic lesion is brought on at the time of greatest cardiac stress and maximal aortic pressure, and these are at their highest during the period of exertion. When no symptoms develop immediately, the diagnosis of acute heart strain is not tenable. If the lesion remains for a time asymptomatic, it must be considered an effect of chronic stress. As closely as pos-

sible this principle of the immediate succession of symptoms following effort should be adhered to in determining the causal bearing of the particular muscular feat upon the subsequent disability.

*Pain*—Pain over the region of the heart or behind the sternum is usually the first development in cases of heart strain. It is characteristically severe, often of a tearing nature, but sometimes sore, aching, knife-like, shooting or burning in character. Or, it may be typically anginal with a sense of constriction across the chest. It is usually localized below the left breast, or may radiate down from the shoulder to the left costal margin, or to the right of the sternum, or down the left arm. It may be severe enough to double the patient over in distress, or for a while be felt merely as a numbness or oppression in the chest.

The significant features about the pain are its close relation in point of time to the muscular effort, and its persistence, or subsequent recurrence after further exertion. If the patient becomes unconscious with the immediate strain, the pain is felt as soon as he recovers consciousness.

*Weakness*—With the pain, there is a sense of weakness which immediately disables the patient from resuming any strenuous work. It may be extreme enough to compel him to sit down or lie down wherever he may be, with a feeling of faintness even on the slightest motion. There may be dizziness and a sensation of darkness before the eyes, and buzzing in the ears. The onset may occur with sudden unconsciousness, the patient falling in collapse when the effort has been ex-

treme. He may faint after a varying period of rest, when he again attempts work.

*Dyspnea and Palpitation*—Associated with the pain and sense of constriction or burning in the chest, there is usually marked shortness of breath. This may appear as an actual gasping for breath which sometimes becomes alarming. It may last for a long time or be more or less temporary with the onset, and recur under the stress of renewed activity. Later, in severe cases, it may become manifestly of the type of cardiac asthma with nocturnal distress, the patient suddenly compelled to sit up breathless for a time.

Palpitation is often felt simultaneously with the occurrence of heart strain. Often there is a marked irregularity due to premature beats. This is exaggerated by effort, such as attempting any work or even walking a moderate distance.

*Disability*—A certain degree of disability and limitation of the field of cardiac response is a cardinal symptom of heart strain. The patient is unable to support any exertion without some degree of distress, pain, dyspnea, palpitation and weakness. While at rest, however, he may be quite comfortable.

*Heart Failure*—In the more severe cases, or in patients who make an effort to continue their work, dyspnea, edema of the legs and other symptoms of heart failure ensue. They are a prompt sequel to rupture of an aortic cusp. Extreme orthopnea or cardiac asthma, and cough may develop due to congestion of the lungs. In most cases, however, these symptoms develop an uncertain number of years after the occurrence of primary heart strain.



*Death From Primary Heart Strain*—Sudden death may occur during or immediately after the performance of extremely severe muscular effort. When this happens, the circulatory system was disposed to a fatal injury by pre-existing disease or weakness which impaired the heart's efficiency. Rupture of an aortic aneurysm or of the heart itself is the usual reason for sudden death due to strain, and death may be delayed even for a few days after this event in rare cases. Due to severe pain alone, death may occur after the onset of heart strain from reflex stimulation of the vagus and cardiac inhibition.

#### PHYSICAL SIGNS

Immediately after the occurrence of heart strain the physical signs will vary from the very slight and equivocal ones of simple tachycardia to those of collapse with great cardiac disturbance, and will depend upon the lesion caused by the strain. The pulse is usually small, feeble and rapid. It is frequently irregular with premature beats, and occasionally very rapid as in an attack of paroxysmal tachycardia. With the progress of time, the area of cardiac dullness becomes enlarged and the sounds may be indistinct and feeble or short and sharp. This, of course, indicates a severe affection. In milder cases, the signs gradually disappear, and the heart becomes apparently normal.

After exertion, the pulse rate quickens and there is manifest shortness of breath. In a large number of cases there is heard a roughened murmur over the apex and aortic area as evidence of an atheromatous change that may have existed prior to the injury.

Tender spots on the chest wall in heart strain are an important and significant sign in these cases, closely related to the complaint of pain. Several tender spots may be elicited usually localized over the ribs in the region of the heart apex or the precordium. These tender areas on the chest wall have a practical clinical value in diagnosis.

Although pulsus alternans occurs only in the very severe cases, the polygraphic tracings will occasionally reveal it when otherwise it might be overlooked. The blood pressure varies and is usually somewhat elevated, both systolic and diastolic.

The electrocardiogram indicates left ventricular predominance. It may show myocardial changes by inversion of the T wave in any of the leads; and in a few cases, intraventricular heart block may indicate myocardial injury.

The vital capacity in these cases is reduced—sometimes only slightly, but with a severe assault, considerably.

It will thus be seen that there are no characteristic features in the physical diagnosis of heart strain. The signs vary with the previously existing heart condition and with the lesion due to the strain.

#### DIFFERENTIAL DIAGNOSIS

In as much as the physical signs of heart strain are not very definitive, no exact conclusions can be reached by considering these alone. When, however, the symptoms and etiologic history are consistent and the physical signs are suggestive and not contradictory, the patient must be given the benefit of the doubt as to disability from strain of the heart.

It is our duty, however, in cases of

alleged heart strain to differentiate between that and other painful affections of the heart. In many cases, it is also necessary to exclude any other condition which will produce the weakness and other distressing symptoms that may have existed prior to an alleged overstress. Irritable heart often gives physical signs which are suggestive; and, in fact, sometimes this condition is the consequence of heart strain. Injury or strain of the pectoral and skeletal muscles must not be interpreted as cardiac in origin. Pain of a reflex, neuralgic nature must also be excluded.

We have therefore to consider not one aspect alone in this condition, but we must weigh in the balance the entire clinical picture, including the etiological factors, the clinical symptoms and the physical signs indicating cardiac change and disability.

#### PROGNOSIS

Heart strain of whatever degree must not be dismissed lightly because in point of time, it is a long enduring condition. The prognosis depends upon the severity of the strain and type of cardiac lesion produced. In general, improvement does not take place sufficiently to enable the claimant to resume a strenuous occupation. The healing processes in such a mobile organ as the heart are very slow. The symptoms persist for an indefinite period and, with strenuous exertion, may be aggravated. Extrasystoles may recur under the provocation of slight muscular exertion.

A period of one year may be assumed for practically total disability during which time the patient must rest completely. Another year is allowed for partial disability, during

which time the patient will be able to do light work. In the more severe cases, the disability may be a total permanent one. In the less severe cases, it may be a partial permanent one. In the milder cases, the patient may be able to resume his work after a year or two. It is difficult to prognosticate in more definite terms.

In arriving at an opinion as to whether a patient is or is not able to work, the gross physical signs alone are often inadequate criteria. The duration of the symptoms cannot be predicted. The forecast should incline toward allowing a long time for recovery to take place. The patient's youth and length of abstinence from work are favorable factors in the prognosis. The prognosis will also depend upon whether the heart was previously sound or not.

#### TREATMENT

For the often severe symptoms of onset of heart strain, the treatment must be symptomatic and stimulating. The patient must be put to bed, his clothes removed, with cold applications to the heart and venesection if there is venous congestion. The acute dyspnea and collapse require stimulants, brandy or coffee, hot baths and mustard pastes applied to chest and back of neck. An intravenous injection of some preparation of digitalis is often marvelous in its effects; it can be followed by subcutaneous injection of some digitalis preparation and epinephrine. Even if the patient rapidly recuperates, complete rest should be enforced as long as possible. Signs of dilatation and a persistently rapid

pulse call for extreme caution and avoidance of all physical exertion.

For the sake of emphasis, the subsequent treatment might almost be summed up in one word—prolonged rest. Some weeks or months are none too long in a mild case for complete physical and mental repose. In general, a period of one year should be allowed for total disability during which time the patient remains under medical supervision and and takes as much rest as possible.

This must, of course, be supplemented by general hygienic measures that are so necessary in the processes of cardiac repair. Moderate doses of digitalis are a great aid in restoring the tonicity of the heart muscle. The time for return to work is indicated in the prognosis above. It may require several years before a patient can resume even ordinary activity. The return from complete rest to full activity must be made very gradually. Light manual work, as sitting at a table without strain or exertion, may be done some months after the accident. The patient can then continue with moderate work such as does not entail heavy lifting, climbing, or strenuous exertion. Often, however, the disability remains total and permanent. This will be best illustrated by the cases appended to this report.

What can be accomplished by care and prolonged treatment is shown by the remarkable results obtained by da Costa in many very severe cases among Union soldiers of the Civil War. Many of these were again able to perform strenuous work and lead active lives after suffering heart-strain.

## HEART STRAIN AND COMPENSATION CLAIMS

In relation to heart strain, "accident", in the meaning of the Compensation Law is held to include some unexpected or unforeseen occurrence of physical or physiological nature arising out of and in the course of workman's employment, which produces a disabling heart condition; aggravates a pre-existing heart condition; or causes sudden cardiac death.

From a compensation standpoint, the previous existence of asymptomatic lesions predisposing to the development of heart strain is immaterial. As an accidental development the liability for the sudden disability of the patient falls upon the acute stress or the immediate exciting cause.

It is very necessary to establish certain criteria and principles upon which the basis of judgment in any particular case must depend. These have to be made sufficiently broad to include all cases in which the causal relationship between the accident and the injury is evident, and yet concise enough to permit of no question in any case that may arise.

Several criteria serve to form a clear cut differentiation in analyzing a particular case:

1. Immediate onset after exertion with
2. Symptoms of cardiac disease.
3. Pain
4. Immediate disability
5. Physical findings.

*First*—The onset of acute heart strain is sudden, immediately following excessive exertion. It is a common but satisfying fallacy on the part of lay people to trace an ailment to a

long antecedent cause. Unless symptoms of heart strain are immediately consequent on the alleged accident, a causal relationship cannot be recognized.

*Second*—Symptoms of a cardiac affection develop immediately, varying from a degree of faintness, momentary dizziness with pallor, to collapse with profuse cold sweat and even unconsciousness. Dyspnea and palpitation may be very conspicuous and the occurrence of irregular heart beats give a sensation of smothering or of a lump in the throat.

*Third*—In all cases, immediate pain referable to the heart or aorta is a prominent complaint. This may be extremely severe and persistent.

*Fourth*—The same exertion as previously endured in the occupation cannot be immediately undertaken. The patient prefers to rest or may do very light work, but finds even that fatiguing. An attempt may be made to resume or continue the routine work, as is only too natural, but strenuous exertion is found to produce distressing symptoms and cannot be continued.

*Fifth*—The suggestive physical signs are discussed above.

#### CASE REPORTS

*Case I.*—William B., a strong negro porter 52 years old, worked at his occupation for twenty-six years. While piling up cases weighing 100-120 lb. each, after severe straining in a difficult and uncomfortable posture, he suddenly became unconscious. He does not know what followed. Immediately on arousing, he felt a sharp, sticking, continuous pain localized in the xyphoid region; he was extremely pale and had a cold sweat. He felt as if dying, was very weak and dizzy, and completely exhausted; he was unable to stand up, had irregular pal-

itation and gasping for breath. After an hour or more, he went by street car to a physician; later he walked up one flight of stairs to his home where he remained abed for one day, and then up and about for one week. At one time, he suddenly fainted.

The pain subsequently moderated; at times, however, it was sharp and severe in the sternal and xyphoid regions even after slight exertion, compelling the patient to rest. He had dyspnea on exertion and palpitation even at rest. Often during the night, dosing off, he suddenly had to rise and even jump off the bed in order to be enabled to breathe. After 10 or 15 minutes, he could lie down again supported on pillows.

Examination revealed the heart apex to be in the fourth space, and the left border four inches from the midsternal line, just inside the nipple. The apex beat was felt slightly. The right border was three inches to the right of the midsternal line. There was a loud overacting first sound with a hollow tone, and ringing accentuation of the aortic second sound. The rate varied between 96 and 120 on different examinations. There were tender spots on the chest wall on the first rib, three inches to the right of the midline, and in the epigastrium, just below the tip of the xyphoid. The blood pressure was 156/98; 144/98; 142/102; 160/110 at various times, with slight pulsus alternans.

The electrocardiogram showed the T wave partially inverted in lead III, and the QRS wave notched in all three leads. The vital capacity was markedly diminished, being about 50% below the normal.

*Summary*—The sequence of events is so definite in this case that one cannot but relate the condition of the heart to the injury that the patient suffered. This case presents characteristically the severe sequel that may occur after extreme physical exertion. It is probable that the same work that resulted in the patient's disability could have been accomplished without

heart strain if it were not for the unusual posture he was in while at work and the poor leverage he could employ in that posture.

It cannot be doubted that a sudden organic change, possibly rupture of fibers at the base of the aorta, or even in the apex of the left ventricle took place. The classical findings of myocardial damage were present ever since the accident, including cardiac pain, tachycardia, extreme weakness, diminished vital capacity, attacks of cardiac asthma, and electrocardiographic changes.

In testing the vital capacity, the patient suffered sudden severe pain in the left scapular region with forced expiration. With repeated attempts at deep inspiration and expiration, there was a progressive diminution in the vital capacity, indicating the exhaustibility of his cardiac muscle after moderate strain.

*Case II.*—Edward A. was a small wiry man and hard worker as a plumber's helper despite his age of 64. While lifting an ice-box, he felt a sudden sharp knife-like pain in the left lower chest, shooting inward below the nipple. He remained in bed after that, unable to move because of the continuous sticking pain in his side. Since then he has had increasing dyspnea and palpitation, worse on exertion. For several nights he had to sit up because of difficulty in breathing. Such attacks have recurred almost daily and sometimes twice daily. At times he felt dizzy and had a tired, weak feeling in the chest. The precordial pain later subsided.

The heart was considerably enlarged. The apex beat was felt in the fifth and sixth interspaces, and the left border was 12 cm. to the left of the median line. The rate, seated was 80, and standing 90, with moderate sinus arrhythmia. The first sound was fair. A systolic blowing murmur was heard over the entire precordium, transmit-

ted up to the vessels of the neck. The aorta did not percuss dilated. Occasional ventricular extrasystoles occurred, sometimes with alternate beats. These increased on exertion or coughing. There was slight tortuosity of the brachial arteries and more of the temporals. The blood pressure was 104/88.

The electrocardiogram showed marked preponderance of the left ventricle. The QRS wave was greatly widened, notched and thickened.

*Summary*—The patient suffered from aortic atheroma and sclerosis of the peripheral vessels. There were also chronic changes in the muscle of the heart, probably consequent on these arterial changes. The functional capacity of the heart was much impaired. The stress of lifting superinduced primary heart strain in a previously diseased myocardium.

*Case III.*—The history of Antonio C., 42 years old, is vivid and significant. For years he was a laborer doing strenuous work. One day, while exerting the utmost effort to lift a heavy stone onto a wheelbarrow, he suddenly felt as if something were tearing in the lower midsternal region. The pain was sharp and knife-like in character, situated below the costal margin in the left axillary line, and in the lumbar spine, and radiated up to both temples. It lasted three to five minutes while the patient remained immobile at his wheelbarrow. He became dizzy; there was darkness before the eyes, a cold sweat on the forehead, weakness and faintness. After 5-10 minutes he made an attempt to move the wheelbarrow, but found himself unable to do so. He then did lighter work for half an hour, ramming the hearth down gently on the repaired culvert.

The patient walked home about a mile, standing at rest every 5-6 blocks, and up one flight of stairs to his bed. The pain in the midsternal region and a peculiar drawing sensation in the temples continued unabated, and prevented sleep.

He remained in bed for four weeks. Dur-

ing this time there were periods of marked weakness and a feeling of tightness across the chest. The pain gradually lessened but did not entirely disappear. At times he almost fainted when standing at toilet or straining at stool. After a month he was able to walk about slowly with pain in the lower sternal region which often increased and forced him to stop to rest. On moderate exertion, he had dyspnea and palpitation, and pain in the temples. He could not sleep on his left side on account of pain.

During the two years that followed the injury, he did light work at times. Once after two hours of work, the pain increased, he became pale and had a cold sweat, and had to be taken to a hospital.

Physical examination at that time showed the left border of the heart at the nipple line 11 cm. from the midsternal line, and the right border 3 cm. from the midsternal line. The pulmonic second sound was distinctly louder than the aortic. The pulse rate was 90 lying down; 96 seated; and 100 standing. The blood pressure was 144/84.

Teleroentgenographic shadow showed the heart to be relatively normal in size and shape, the left border reaching almost an inch inside the left nipple or midclavicular line. The descending portion of the arch was somewhat prominent. The ascending portion of the aorta appeared moderately wide.

The vital capacity was moderately less than normal.

Hopping fifty times on one foot (1080 foot pounds of work) induced a heart rate of 140. After two minutes, the rate was still high, 110 per minute. The heart action after exercise was forceful with a systolic shock.

The electrocardiogram showed left ventricular preponderance. The R wave was notched in its initial phase in lead II, and in its terminal phase in lead III, making the QRS interval wider than normal. The T wave was isoelectric in lead III.

*Summary*—The history in this case speaks for itself. Something happened as a result of excessive physical effort from which complete recovery

had not taken place after two years. The patient still suffered from pain especially after exertion. With greater effort, pallor, cold sweat, and increase of pain compelled the patient to rest.

Although the heart was not enlarged, the electrocardiogram suggested the possibility of subendothelial damage in its wall. The aorta showed slight widening. The blood pressure was normal. The rate was increased, except after long repose. Exercise induced a hyperactive heart beat.

It is difficult to define precisely the lesion in this case. Strain increased the pressure in the aorta and if it was extreme, it may have caused a tearing of the elastic and connective tissue fibers in the wall of the aorta.

*Case IV.*—Sebastiano P. 45 years old, worked as a laborer without difficulty until one day, when attempting to lift a heavy stone, he felt pain in the left chest which compelled him to sit down to rest. He also developed a traumatic hernia in the left groin for which he was operated on a month later under general anesthesia. Following the injury, he had shortness of breath even at rest, palpitation, and occasional sticking pain in the lower precordial region after exertion.

Three months later, his heart showed a well developed chronic mitral stenosis. There was a sharp systolic shock at the apex. In the left lateral posture there was also a presystolic thrill and rumble. The blood pressure was 152/100.

It is significant that the electrocardiogram did not show the usual graphic result of long-standing mitral stenosis. The P wave was small, indicating the absence of hypertrophy, and the other waves did not show any particular abnormality. There was left ventricular preponderance with a marked effect of respiration on the R wave in lead III. The heart rate was 120, the effect of his cardiac deficiency.

*Summary*—The case presents considerable difficulty because of the presence of a number of associated factors. There are first, the hard work the patient was doing before the injury; second, the development of a traumatic hernia which indicates severe physical strain; third, the presence of a chronic valvular heart lesion; fourth, the uncertain effect of the anesthesia during the herniotomy; and fifth, the rapid progress of the condition after that, totally incapacitating the patient.

The definite findings from which the rest of the case must be constructed consist of a well-developed mitral valvular lesion with myocardial weakness which has lasted an uncertain period of time. Judging from the lack of evidence at the time of operation that the patient's heart was affected, we must assume that before the alleged accident the patient's heart was in normal condition, or at least in condition adequate for the conduction of his duties and occupational labors.

This implies the development of the heart condition from and after the time of the accident. The history asserts the occurrence of pain in the left chest following the accident. How much of an effect upon the heart was produced by lifting of the stone is problematic and cannot be determined exactly. But that there was some effect must be judged from the sequence of events.

Upon the preliminary strain of the heart was superimposed the strain and toxic influence of general anesthesia one month later. Then the cardiac symptoms increased so that after three months, there was beginning cardiac failure with marked shortness of

breath, palpitation, distress on even moderate exertion, flushing of the cheeks and lips with slight cyanosis, and evidence of pulmonary engorgement.

With the usual mitral stenosis of long-standing, there is commonly a history of rheumatic fever or other infection. The condition usually progresses slowly and heart failure does not take place in such a short time as in this case without evidence of acute involvement. In this case we have no adequate history, except that associated with the accident, to account for the organic condition present.

Usually also, in chronic rheumatic mitral stenosis, the electrocardiogram indicates a hypertrophy of the auricles by quite characteristic changes in the *P* wave. Here, again this is absent indicating a rapid change in the mitral valve and auricles.

In a critical analysis of this case, we are therefore compelled to assume a causal relationship between the alleged accident and the eventual cardiac failure. The intervening anesthesia no doubt contributed to the damage and must be considered as part of the alleged accident.

*Case V.*—Mountainy M., 25 years old, was a helper on an express wagon. While swinging a bale of paper weighing 180 lb., he was compelled to support it in a strained posture while pushing it high up on the end of the wagon. He had a feeling of numbness in the left upper abdomen. After working a little, he felt extremely faint; this recurred a few times during the succeeding days. He traveled home feeling faint and dazed, with numbness in the left side. As he walked up four flights of stairs, he had a feeling of soreness across the upper abdomen and extreme weakness.

Since then, he has had occasional peculiar

irregular heart beats. Nine days after the accident, he attempted to work at his previous occupation but could not lift anything heavy on account of immediate faintness. In one of these attacks, he actually fainted with sticking and pressing pain just below the left breast, and vomiting. After moderate exertion, he was fatigued and had dyspnea and palpitation.

The heart was not enlarged; the sounds were good. There were tender spots on the fifth and sixth ribs three inches to the left of the midline. The blood pressure was 140/70. The electrocardiogram was negative.

#### SUMMARY

Immediately after exertion, the patient felt a peculiar sensation in the left side of the upper abdomen, and enough discomfort to desist from further work. He then experienced faintness, weakness and other sensations attributable to the circulatory system. Later, after moderate effort, he had slight dyspnea, palpitation, and a feeling of fatigue.

Although there were no other physical signs of cardiac involvement, there were tender spots on the chest wall located over the fifth and sixth left ribs. Otherwise, the main reliance must be placed upon the slight symptoms present.

The casual relationship of the particular over-stress recorded to the heart-strain that ensued is evident.

*Case VI*—Fred R., a mechanic 37 years old, was pulling a heavy wind organ, when he was suddenly seized by a severe sharp, momentary pain localized below the left nipple, and a sense of suffocation. He rested seated for about two hours, with a feeling of extreme weakness and tenderness below the left breast. The next day, he undertook only supervising and stopped work after several hours.

Since then, he had dyspnea and palpitation, and a dull precordial pain after exertion such

as climbing steps or crossing a street rapidly; and he often felt irregular heart beats.

Physical examination five months later showed the heart enlarged to the left and rather rapid, 90 beats per minute. The apex beat was just beyond the nipple line in the fifth space, in which region there was a tender spot on the sixth rib. The blood pressure was 122/82.

From the available tables the patient's vital capacity was 25% below the normal. The electrocardiogram gave no data of interest besides a tendency to preponderance of the left ventricle. Teleroentgenographic shadow showed slight enlargement of the heart both to the left and right, but the aorta was of normal width. There were signs of mild hyperthyroidism with slight digital tremor. A year later the basal metabolic rate was +20.

#### SUMMARY

The patient was suddenly seized by a sharp pain in the region of the heart apex with a feeling of suffocation and extreme weakness. Subsequently he had a tender spot on the precordium and pain, dyspnea, and irregular heart action after exertion. A myocardial change was produced by strain, and in the process of healing there was hypertrophy of the left ventricle.

*Case VII*—Hyman K., aged 21, a shipping clerk of small build, while moving a case weighing 700-800 lbs., felt a sticking pain shooting across the precordial region to the right of the sternum. This recurred whenever he lifted something heavy. He also developed moderate dyspnea and palpitation on exertion.

The heart was found slightly enlarged. Its left border percussed just outside the nipple line. There were tender spots over the fourth and fifth left ribs and over the left border of the heart. The blood pressure was 146/100. X-ray showed the heart slightly prominent to the right. The electrocardiogram was negative.

#### SUMMARY

Immediately following lifting, the patient had a sticking pain in the pre-



cordium. This recurred in a lesser degree when the strain was repeated, and indicated some effect, organic in nature, upon the heart and aorta. The casual relation of the effort to the cardiac pain is obvious in this case.

*Case VIII*—Emil O. was a robust iron worker 59 years old. While lifting the end of an iron railing weighing 1500 lbs., he suddenly felt a severe, sharp, burning pain radiating from the right upper abdominal region, obliquely to the precordial and left pectoral regions. He screamed with pain and distress, unable to catch his breath, with darkness before his eyes. He was assisted by two men to a hospital where he remained under observation for two weeks. The pain across the front of the chest persisted, somewhat moderated, but increased with exertion.

The heart was found slightly enlarged to the left, its border being beyond the nipple line. The apex beat was barely palpable, and the sounds were of poor muscular quality. There was a tender spot on the third and fourth ribs, 2 inches to the left of the midsternal line.

The blood pressure, on different occasions, was 200/112; 236/110; 220/118, with distinct pulsus alternans. The liver was considerably enlarged below the free border and there was moderate pretibial edema. The vital capacity was greatly reduced. The electrocardiogram showed right bundle branch block.

#### SUMMARY

Suddenly, following great strain in lifting, the patient had the typical pain and other symptoms which indicate strain of the heart muscle. We must assume from the labor in which the patient was engaged, that his heart condition was at least able to endure the strain of his occupation. Without doubt, certain arterial changes that come with age had already initiated changes in the myocardium, but these

were not sufficient to disable the patient in any way. It can definitely be asserted that the heart strain in this case resulted directly from the injury, as an aggravation of his previous condition.

*Case IX*—Charles W. is an electrician 26 years old. While lifting a transformer weighing 150 lbs., he felt a sudden sharp knife-like pain along the nipple line from the left shoulder down to the lower left costal margin, with a sudden, quick and irregular beating of the heart, both of which lasted about two minutes. He remained standing for a few minutes, immobilized by the pain, but continued to work more moderately, feeling fatigued.

The pain returned that night after supper, as a steady pressing sensation just below the left nipple region; it lasted all night and was associated with some palpitation. In the morning, the pain was greatly relieved, but it recurred two days later as a dull pain over the lower precordium. The patient remained at home and abed for two weeks, and then returned to lighter work.

Since then he has dyspnea, rapid heart action and palpitation on ascending hilly ground, or after moderate exertion such as his present work requires—which consists of climbing poles. Recently, dizziness and scotomata appear after exertion, but never faintness. The pain has recurred three or four times and is relieved by resting for about an hour.

The heart was not enlarged, and presented a normal systolic impulse. There were frequent ventricular premature beats, most of these not transmitted to the radial pulse. The aortic second sound was less marked than normal. The rate seated was 72, including extrasystoles; standing, it was 80. The blood pressure was 126/86. The extrasystoles showed very low pressure. The vital capacity was 11% below the normal.

The electrocardiogram showed frequent ventricular premature beats arising from the base of the right ventricle. The premature beats occurred early, producing no effect on the radial pulse.

## SUMMARY

The sequence of events is so definite in this case that one cannot but relate the condition of his heart to the injury that the patient suffered. Some definite organic change resulted from the excessive sudden strain which he endured at the time of his accident. It is not usual for a heart which has suffered from a strain of this character to undergo absolute restoration to normal.

*Case X*—Joseph D. was a laborer 36 years old. While helping support the end of a heavy iron pipe on his left shoulder, he felt a slight pain or soreness in the left chest, from the shoulder down to below the breast. This became worse when he was relieved of the weight, with a feeling of faintness. The pain persisted; the patient did lighter work for the day, but remained at home subsequently, complaining of dyspnea and palpitation on exertion, and of continuous aching pressing pain in the precordial region. He could not sleep on the left side with comfort.

On examination, the heart was not enlarged. Over the apex, the first sound had a peculiar hollow quality. There was a slightly tender spot over the fourth rib, four inches to the left of the median line.

The vital capacity was very much reduced. The blood pressure was elevated—142/104; 158/114. X-ray showed slight dilatation of the ascending arch of the aorta. The electrocardiogram showed left ventricular preponderance. The T wave was inverted in lead III and the P wave was notched in lead II.

## SUMMARY

During strenuous effort, the patient felt pain and soreness in the left chest. This persisted and was subsequently associated with dyspnea and palpitation. The symptoms developed before the presence of obvious physical signs. When the symptoms are consistent, as in this case, and the physical signs are suggestive and not contradictory, the

patient must be given the benefit of the doubt as to his disability from strain of the heart.

*Case XI*—John B., a robust and rather plethoric man of 60, was trapped in a small room by a fire in the exit. He became greatly excited, and endeavored to pull apart the iron bars across the windows in the room. In doing so, he struggled frantically. He remembers being dragged away from the window in a semi-conscious condition, quite exhausted from his attempts to escape. He was extremely dyspneic and had a sticking pain in the left sternal and precordial regions, or a sensation of heaviness in the lower sternal region.

Following the accident, he remained in bed for eight days with weakness, dyspnea and cough. Since the accident, he had dyspnea on moderate exertion with palpitation after walking 5-6 blocks. Orthopnea was present.

The heart was slightly enlarged to the left, its left border being outside the nipple line. Aortic dullness was  $1\frac{3}{4}$  inches to right of the midsternal line. The sounds showed deficient muscular quality. The blood pressure was 192/100, and the vital capacity was 36% below the normal.

The electrocardiogram showed left ventricular preponderance. The QRS wave was widened to 0.12 seconds.

## SUMMARY

In the distress and alarm which occurred during an accident, the patient exerted extreme physical effort in an attempt to save his life. During this, he suffered symptoms referable to his heart as well as to the skeletal muscles (Left inguinal traumatic hernia).

A moderately advanced myocardial condition with high blood pressure apparently existed before the accident. It is however doubtless that there occurred an aggravation of the condition. This takes a long time to ameliorate. The patient's dyspnea was improved considerably several months

after the accident and he could undertake moderate physical activity.

*Case XII*—George K., a cook and counter-man, 30 years old, had worked at his occupation for several years without discomfort. One day, while carrying a bag of sugar weighing 100 lbs. up one flight, he felt a tearing pain below the left breast, radiating to the region of the navel. With this, there were weakness, marked pallor, cold sweat and vomiting. He remained seated for two hours without relief. For the next three weeks, he was in bed with dyspnea, palpitation, and continued pain. After returning to work for several hours, the symptoms recurred. Subsequently he also had occasional attacks of extremely rapid heart beating of sudden onset, lasting a varying period of time.

The heart showed a heaving apex impulse far to the left and below its normal position. The enlargement was also evident to the right. Over the apex there was a faint systolic thrill and murmur transmitted upward to the aortic area. There was a marked loud, prolonged, blowing diastolic murmur over the aortic area replacing the second sound and transmitted down along the sternum. A presystolic "Flint" murmur was also audible. There was unusually marked tortuosity of the temporal and brachial arteries, and a Corrigan and capillary pulse. The blood pressure was 134/62, and the vital capacity was considerably below normal. The Wassermann test was positive.

X-Ray showed the heart enlarged in all its diameters, with accentuation of the right auricular and left ventricular curves.

The electrocardiogram showed left ventricular preponderance and numerous premature beats arising from two separate foci—one in the left base and the other at the right apex.

*Summary*—For three and a half years the patient pursued the same occupation without any difficulty or complaint. At the time of the alleged accident, there suddenly developed symptoms indicating a sudden tearing lesion within the chest. The symptoms were severe and have practically

disabled the patient permanently. Each attempt at work is followed by distress with the need of hospital care, and attacks of paroxysmal tachycardia often occur.

It is evident, however, from the physical examination that there was a premature development of advanced arteriosclerosis involving the peripheral arteries and arterioles. There was an excessive degree of vascular change rarely seen at the patient's age.

The physical signs showed a marked aortic diastolic murmur which could be produced by rupture of the aortic valve. The valve was doubtless diseased prior to this, but muscular strain may have caused the sudden development of aortic regurgitation.

The causal relationship between the accident and the development of the aortic regurgitation is direct in this case. Accepting a pre-existing arteriosclerosis, rupture of an aortic valve in consequence of sudden muscular strain is an accident which is not very uncommon. It does not usually occur in a previously normal valve, but in one damaged by a pre-existing atheroma and fibrosis due to arteriosclerosis, syphilis, or other degenerative disease. The Wassermann test in this case indicated a possible luetic cause for the entire condition.

*Case XIII*—Frederick F., aged 47, did very hard labor driving a truck and lifting cases of 500-900 lb. each. One morning after working he became dizzy and felt weak, and on his return to the place of business he could hardly stand up. There was no chest or abdominal pain. The patient returned to work after two days and continued at work for four months.

Since the onset, however, he felt fatigue and dyspnea after exertion, but no pain. Three months after the accident, he developed swelling of the feet and legs, marked

orthopnea and a distressing cough which was worse on lying down.

The heart was enlarged to the left, the apex being in the fifth space outside the nipple line. The right border was 5 cm. from the midsternal line. The aorta was widened. There was an audible third heart sound due to auricular systole. The rate was 114, with frequent ventricular extrasystoles. The blood pressure was 160/120 with marked pulsus alternans. The axillary, inguinal and epitrochlear glands were enlarged. The vital capacity was 60% below normal. A blood Wassermann test gave a ++++ reaction.

The electrocardiogram showed left ventricular preponderance, low voltage, and an occasional ventricular extrasystole arising from the right base.

*Summary*—The patient suffered from chronic myocarditis with high blood pressure and marked pulsus alternans. Physical examination indicated a failing heart with congestion at the bases of the lungs and marked edema of the legs. The pathological condition in the heart was syphilitic and did not depend in this case upon, or have any relation to his work.

*Case XIV*—Frank S., aged 40, was a laborer. While hoisting a large tube of concrete weighing between 300 and 500 lb. by hand, he felt a severe aching pain in the lumbo-sacral region and spine which prevented him from continuing his work. After coming home, he felt a smothering sensation with very rapid palpitation and a feeling of heaviness across the lower sternum. He was in fear of dying. These symptoms gradually subsided after four days.

He then had palpitation after walking a short distance or upstairs, occasional dyspnea and weakness during the night, with a feeling of smothering.

The heart was not enlarged. The first sound was deficient in muscular quality; at the apex there was a soft short blowing systolic murmur not transmitted. The heart rate was 60 per minute, and the blood pressure was 122/68. The vital capacity was below normal. The electrocardiogram was negative. X-ray showed a "drop heart."

*Summary*—The symptoms of dyspnea and palpitation may be due to the patient's heart condition. The pain the patient experienced in the lumbo-sacral region was interpreted on the basis of a spinal arthritis. The other cardiac symptoms were the result of heart strain due to the recorded accident.

*Case XV*—John G., a man of 32, was a helper on a truck. His work consisted of carrying loads of brick of 50 lb. or more. For six months prior to his present illness he had dyspnea and palpitation on exertion. In the course of his work he felt momentary darkness before the eyes and faintness and headache. One day he began to feel a slight sticking pain in the region of the left breast. Since then he had occasional localized sticking pain in the left chest.

His heart showed a rough blowing systolic murmur over the apex and aortic area. The peripheral vessels were slightly tortuous. The Wassermann test was negative. The blood pressure was 144/88. The electrocardiogram was negative.

*Summary*—A patient with cardiovascular disease would naturally feel symptoms of distress if he undertook a strenuous occupation. The patient had symptoms of cardiac distress for six months prior to his complaint which his work naturally aggravated.

It is probable that in consequence of the repeated liftings and pullings there was a cumulative effect upon the heart and aorta. The aortic condition was of long standing, which the work temporarily aggravated.

There cannot be assumed any causal relationship between his work and the cardiac condition that the patient suffered previously. The occupational stress may have aggravated his myocardial deficiency. But from a compensation standpoint there was no accident as a factor in the production of heart strain.

# Polycystic Disease of the Kidneys

By GEORGE MORRIS PIERSOL, M.D., *Philadelphia, Pennsylvania.*

Although polycystic degeneration of the kidneys cannot be looked upon as a rare disease, it may be regarded as relatively uncommon. Therefore, it seems justifiable to add to the group of reported cases.

The frequency with which polycystic disease occurs may be judged from the following statistics. In 1887 Neumann (1) reported fourteen bilateral and two unilateral cases in 10,177 necropsies. Preitz in 1905 working up the Kiel Institute material found sixteen cases in 10,000 autopsies. Bugbee and Wolstein (2) in 4903 autopsies on children, recorded twenty cases. In 1927 Gruber at Jena collected eight bilateral cases in 3,500 postmortem examinations. During the past three years only five instances of the condition have been found in the necropsy material at the Philadelphia General Hospital. At the Boston City Hospital, Garceau met with ten cases in 2,439 necropsies. A few years ago Barnett was able to collect a total of 251 cases. Since then 238 additional cases have been recorded. An idea of the frequency with which polycystic disease of the kidney is met with in our large general city hospitals may be gained from a statement made by Atonna and Morrissey (3), that during the four years from 1922 to 1926 inclusive, the total number of cases re-

ported from the hospitals of New York City averaged only eight per year.

Two striking examples of this disease recently encountered awakened our interest in this condition.

The first case was that of an Irish laborer, aged 42 years, admitted during the winter of 1927 to the writer's service at the Philadelphia General Hospital. His outstanding symptoms were swelling of the abdomen, pain in the left upper abdominal quadrant, swelling of the legs, cough and dyspnoea.

The patient stated that he had always been unusually well until August, 1926, when he developed acute abdominal pain, was taken to a hospital in Philadelphia where his appendix was removed. From that time on he had been sick, complaining of the above noted symptoms. His strength failed so that for the four months prior to admission, he was unable to work. He had also developed since his operation, a decided nocturia.

Aside from the fact that he had been for years a heavy drinker, there was nothing significant in his previous medical or social history. His family history was also unimportant. There was nothing to suggest the existence of polycystic kidneys in any of his forebears.

It is interesting to note that a report on his operation in August, 1926, from the hospital where it was performed, states that a somewhat inflamed appendix was removed, that his liver was enlarged, contained multiple cysts, the lower border being four to five inches below the costal margin. The appendix was removed, and an hepatic cyst was punctured and drained. The patient made a fair recovery and was discharged

with a diagnosis of Hepatic Cyst; Impending Cirrhosis of the Liver.

The salient features of our physical examination of this patient were as follows:—

The patient was a well developed, but rather poorly nourished white male. There was a left peripheral facial palsy due to a severe head injury in 1920. The lungs were normal except for some crackling râles at the right base. There was a distinct widening of the costal angle due to the marked outward flare of the lower ribs as from pressure. The apex beat was visible and palpable in the fifth interspace on the left mid-axillary line. Percussion showed decided left sided cardiac enlargement. The aortic second sound was louder than the pulmonic. At the apex a soft, non-transmitted systolic murmur was heard.

Chief interest centered in the abdomen. There was distinct bulging of the left side of the abdomen and of the left flank. A marked ventral hernia was present. The liver was enlarged, hard, non-tender and was palpable two inches below the costal border. The left side of the abdomen was filled with a large, hard, irregular, tender mass. This mass extended down to the left iliac crest and toward the mid-line to within two inches of the umbilicus. It moved with respiration, was definitely palpable bi-annually and caused marked fullness in the left flank.

A summary of the laboratory examinations is viz:—Urine: acid, clear, Sp. Gr. 1006-1010. All specimens contained definite traces of albumin. Glucose was always negative. Microscopically no casts were found, but leucocytes and a few red blood cells were always present.

On admission his hemoglobin was 55%; RBC. 2,950,000; leucocytes 7,200. Polymorphonuclears 76%, Lymphocytes 24%. In several subsequent differential counts the eosinophiles were increased, ranging from 2 to 5 per cent.

His blood Wassermann was negative to all antigens. His blood sugar was 155 mgms. per 100 c. c. of blood. The urea nitrogen was 40 mgms. per 100 c. c. of blood. On the day of admission his temperature was normal, his pulse slightly increased and his systolic blood pressure 130; diastolic 60.

A tentative diagnosis of Cirrhosis of the Liver, or Banti's Disease was made.

Three days after admission the patient had a generalized convulsion epileptiform in character. After this he became toxic, semi-stuporous and vomited repeatedly. There was no hematemesis. He became obstinately constipated. His toxemia improved, but the vomiting, especially after taking food, continued. Pain in the left side of the abdomen increased and the mass became larger and felt more nodular.

With the thought of gastro-intestinal malignancy in mind, a fractional gastric analysis was done. This showed a total absence of free hydrochloric acid, but no blood. A fluoroscopic examination of the gastro-intestinal tract showed *no* organic lesion of the stomach, which was displaced to the right, but a herring bone appearance of the jejunum thought to be due to either pressure of adjacent organs or an obstructive lesion at the jejuno-ileal junction.

In as much as the vomiting continued and the patient's condition was growing steadily weaker, a surgical consultation was held and surgical intervention advised.

An exploratory laparotomy was done under nitrous oxide anesthesia. The liver, spleen and gall bladder were found normal. The abdomen was found almost filled by two large retro-peritoneal polycystic masses. In spite of nine months of varied observation the correct diagnosis of congenital, bilateral, polycystic kidneys was then made for the first time.

Within twenty-four hours after operation the patient died of bronchopneumonia with pulmonary edema. An autopsy was performed. The essential findings at autopsy were as follows:—

The heart was moderately enlarged due to left ventricular hypertrophy. The mitral valve was normal. The coronary arteries showed a slight degree of atherosclerosis. The aorta showed a moderate degree of arteriosclerosis. Both lungs were the seat of old pleural adhesions and of recent congestion, edema and bronchopneumonia. When the abdomen was opened, a striking picture was presented. Both kidneys were seen to be markedly enlarged and cystic. They occupied most of the abdomi-

nal cavity. Each kidney extended from the pelvic brim to the dome of the diaphragm. This is well shown in the photograph taken with the kidneys in position. (Fig. 1.) The left kidney weighed 1450 gms., and measured 33x18x13 cm. The enormously enlarged kidney was made up

being largely replaced or compressed by the multiple cysts.

The spleen was somewhat enlarged, soft, and congested. The adrenals were plastered on to the upper poles of the kidneys and appeared quite normal. The liver was about normal in size, weighing 2050 gms.

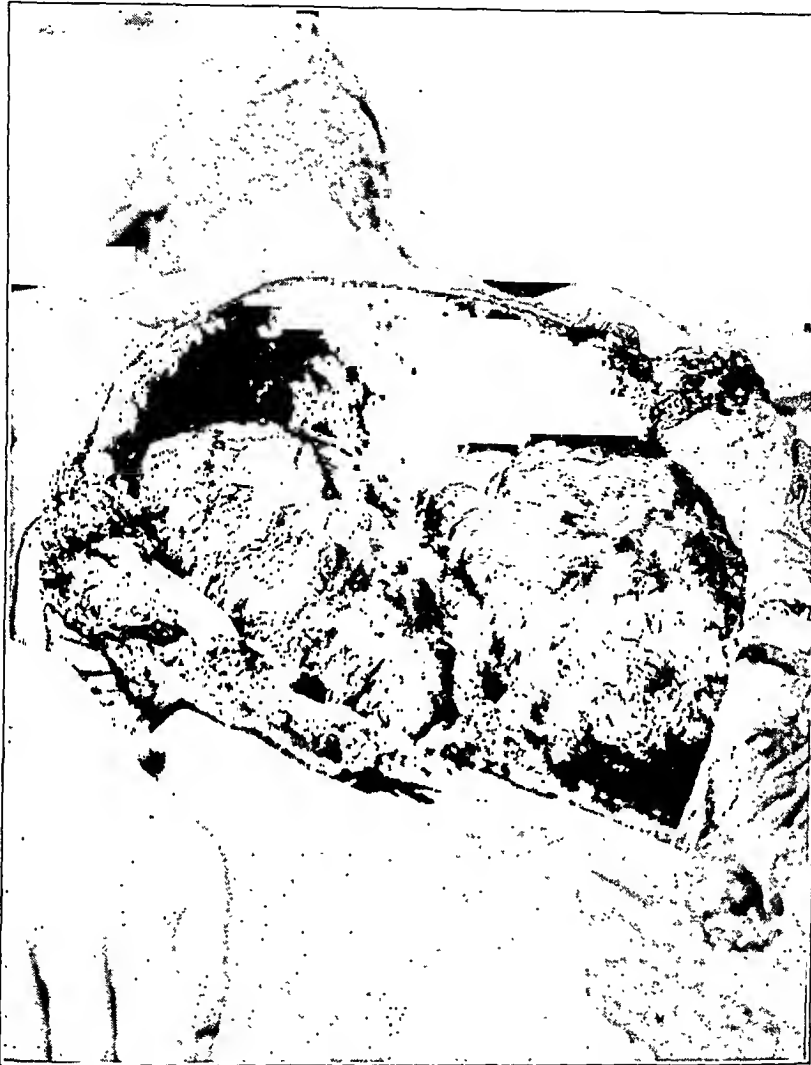


FIG. 1.—Enormous bilateral polycystic kidneys filling almost the entire abdominal cavity.

of innumerable cysts of varying size. The largest cyst measured 5x6 cm. in diameter. The right kidney weighed 2970 gms.; was fully as large as its fellow and was identical in structure, being largely converted into a mass of various sized cysts. Upon section little normal renal structure remained in either kidney, the normal parenchyma

Its capsule was smooth, the lower margin fairly sharp. On section two small cysts were revealed each about 1.5 cm. in diameter, with thin walls and containing clear fluid. The remainder of the gastro-intestinal tract was negative.

The final anatomical diagnosis was,

Congenital Polycystic Kidneys; Cysts of the Liver; Moderate Arteriosclerosis and an Hypertrophied Heart.

The autopsy clearly proved that the masses which had been palpated during life, and were regarded as an enlarged liver and spleen, were actually the two large polycystic kidneys. The liver and spleen were never palpable.

In this case a correct clinical diagnosis was never made until after exploratory operation. We failed to interpret correctly the abdominal signs. We overlooked the possible significance of the hypertrophied left ventricle, the accentuated aortic second sound, and the evidence of arteriosclerosis. Our minds were so fixed on other diagnoses, that no one gave proper weight to the persistent albuminuria, the occasional red cells in the urine, or the definitely increased blood urea nitrogen. If these findings that pointed to kidney involvement had been given due consideration, the existence of renal tumors might have been suspected and proved by pyelography and functional kidney tests.

The second case occurred upon the service of my associate, Dr. H. L. Bockus, at the Hospital of the Graduate School of Medicine of the University of Pennsylvania. I am indebted to Dr. Bockus for the opportunity to study and report this case.

The patient was a business man, aged 64 years, who was admitted on 11-14-1926 as a suspected case of pernicious anemia or carcinoma of the intestinal tract. His chief complaints were weakness, nausea, vomiting, loss of weight and anemia. For eighteen months he had had gastro-intestinal symptoms, with the exception of one attack of alleged renal colic in August, 1925. This cleared up and he had no further renal

symptoms. Three months before admission his nausea and vomiting became persistent. He lost weight and complained of numbness and tingling in the extremities.

On admission the outstanding features of his physical examination were marked pallor, a definite mouth infection, infected tonsils, a chronic glossitis, marked left ventricular hypertrophy, an accentuated aortic second sound, palpable vessels and decreased knee jerks. The abdomen was soft and relaxed. The liver and spleen were not palpable. On the right side of the abdomen along the line of the ascending colon and clearly not connected with the liver, was a mass the size of a small apple lying rather superficially and easily palpable. At the time this was looked upon as a carcinoma of the colon.

The laboratory findings soon put a different aspect on this case. On admission his systolic blood pressure was 218, diastolic 165. The urine had a specific gravity varying from 1008-1010, contained a heavy cloud of albumin, but no glucose and no casts or red blood cells. The hemoglobin was 32, erythrocytes 1,900,000 and leucocytes 5,300, with a color index of 0.8; polymorphonuclears 87%, lymphocytes 11%, transitionals 2%. There were no nucleated red cells nor any blood findings suggestive of true Addisonian anemia. The blood Wassermann was negative to all antigens. The first blood chemistry showed the blood sugar to be 87 mgms. per 100 c. c.; uric acid 3.5 mgms.; creatinin 14 mgms.; urea nitrogen 160 mgms.; cholesterol 130 mgms., and chlorides 496 mgms. A subcutaneous phenol-sulphonphthalein test showed no dye eliminated. Later when the dye was injected intravenously, 12½% per cent was recovered at the end of the first hour, and a like amount at the end of the second hour. A fractional gastric analysis showed normal gastric function, free hydrochloric acid being present in considerable quantity. An x-ray study showed a dilated aorta, a normal stomach and small intestines and a colon pushed down by a mass that was obviously not related to the bowel.

The blood findings and gastro-intestinal studies clearly eliminated the possibilities of pernicious anemia or intestinal malignancy.



All the clinical and laboratory findings pointed clearly to renal insufficiency in a chronic nephritic with hypertension.

Further progress of the case bore this out. The patient became progressively more anemic and weaker. Five days after admission he was stuporous, had a uremic odor to his breath, and his blood urea nitrogen was up to 164 mgms. per 100 c. c.; creatinin 30.4 mgms. and the CO<sub>2</sub> of the plasma equalled 27 vol. %. A transfusion was done with little success at this time. He continued to become more toxic and died in uremia three weeks after admission. Three days before death his creatinin was 21.2 mgms. and his urea nitrogen was up to 170 mgms. per 100 c. c. of blood.

During the entire course of his illness the mass in the right upper abdomen was constantly palpable and a less distinct mass could at times be felt in the left side. A week before death he was seen by Dr. J. B. Carnett in consultation, who suggested the diagnosis of bilateral polycystic disease of the kidneys because of the somewhat cystic feel of the right-sided mass, the exclusion of all other explanations for the abdominal mass, and the co-existence of hypertension and renal insufficiency.

The significant features of the autopsy in this case were:—Healed tuberculous lesions with adherent pleura at the apices of the lungs with terminal congestion and edema. There was slight cardiac hypertrophy with chronic fibrous interstitial tissue increase. The gastro-intestinal tract was negative. The liver was not enlarged, but contained a few small cysts. The spleen was not enlarged but was the seat of chronic fibrosis. The masses felt were a pair of definitely enlarged, congenital polycystic kidneys. The right kidney weighed 1095 gms., the left kidney 890 gms. Both kidneys contained innumerable cysts of varied size. These cysts were lined with low cuboidal and even flattened epithelium. The tissue be-

tween the cysts contained Malpighian bodies and tubules and was the seat of chronic interstitial nephritis.

The fluid from the cysts examined postmortem, was slightly turbid and contained *non*-coagulable nitrogen fractions in the following amounts. Uric acid, 20 mgms. per 100 c. c.; urea nitrogen 300 mgms. per 100 c. c. and creatinin 58 mgms. per 100 c. c.

In this second case the evidence of renal involvement was much more definite than in the first, but the abdominal tumors were much less obtrusive. As in the first patient, the original diagnosis was wrong and it remained for a surgeon to make a correct one.

Polycystic degeneration of the kidneys may be roughly divided into four groups.

1st. Those in which the condition develops at or shortly after birth. These children die promptly after birth. In this group the condition is usually associated with other developmental defects as cleft palate, imperforate anus, cysts of the ovary, supernumerary digits, etc. In the other groups the condition does not manifest itself until adult life.

2nd. The second group presents nothing that suggests the existence of polycystic kidneys. In this type renal insufficiency develops unexpectedly and is promptly fatal. The true nature of the renal lesion is only discovered at autopsy.

3rd. Group three shows the usual manifestations of chronic hypertensive nephritis often associated with progressive weakness and a marked secondary anemia. The polycystic renal degeneration is only recognized when the kid-

neys become expanded and are definitely palpable cystic tumors. Most of the cases recognized clinically have been in this group. The second case here reported clearly belongs in this class.

4th. The fourth group comprises those cases in which the first symptoms point clearly to urinary tract disease such as a definite renal tumor, hematuria, renal colic, persistent fullness, pain and dragging in the ilio-costal space. These cases are usually recognized more easily and earlier. Our first case more nearly fits into this group.

According to Cabot's series, the greatest number of cases of polycystic renal degeneration presents symptoms between the fortieth and sixtieth years. The tumors are rarely found after infancy until the eighteenth or twentieth years are passed.

The condition is said to be more common in women than in men. Heredity seems to play a definite rôle in its production. In 1902 Osler reported a family in which the disease occurred repeatedly in different members. Crawford (4) reported a case in which the disease had occurred with amazing frequency in various members of the patient's family. He quotes Borelius and Love and Richmond, as having made similar observations.

The condition is more often bilateral than unilateral. Sieber (5) found only 10 unilateral cases in 150 cases proved by autopsy. In adults the most commonly associated pathological conditions are cysts of the liver, arteriosclerosis and cardiac hypertrophy.

The diagnosis depends largely upon finding in one or both flanks, irregular,

nodular tumor formations having the general outline of the kidney. When the renal tumors are bilateral the diagnosis may be made with certainty, as polycystic disease is practically the only cause for bilateral kidney tumors. These tumors may exist for years without symptoms. As a rule, however, albuminuria with other evidences of chronic renal disease develop. Hematuria irregularly intermittent is reported in fifty per cent of cases. When present it is an aid to diagnosis. Pyelography, especially advocated by Atonna and Morrissey (6) and functional kidney tests are useful procedures in arriving at a diagnosis. The former is particularly helpful in differentiating polycystic disease from hydronephrosis, pyonephrosis and hypernephroma. In many cases, especially those in which the tumor is inconspicuous, the diagnosis is difficult and frequently unsuspected.

The prognosis in polycystic disease of the kidneys is ultimately uniformly bad. The earlier the age of onset the worse the prognosis. It is rare for adults to survive more than from one to ten years after symptoms develop. The majority of adults succumb in their fourth decade.

The treatment of the condition is thoroughly unsatisfactory and is largely medical. The bilateral nature of the disease makes nephrectomy out of the question. In twenty-two cases nephrectomy was attended by a mortality of 31.89% and only two cases lived beyond two years. Roving (7) has advocated puncture and drainage of the cysts for the relief of pressure. His results, however, were of only temporary benefit. Renal infection,

urethral obstruction and stone may demand radical surgical interference. On the whole, it is safe to say, that the majority of cases will live as long and do as well under palliative medical management.

The pathogenesis of the polycystic kidney has always aroused considerable interest. Virchow held that the uriniferous tubules of the kidney become blocked off as the result of inflammatory tissue in the renal papillae thus causing true retention cysts. This theory has few, if any, advocates today.

Another group of pathologists contended that the cysts are new growths and that they are virtually cyst-adenomata. Subsequent observations have failed to substantiate this view.

The theory that today is most generally accepted is that the cysts are the outcome of a developmental defect. Recently Kampmeier (8) has carried on

extensive embryological studies on the origin of congenital renal cysts. His conclusions in brief are as follows:—"Every human individual during fetal life normally passes through a period characterized by the presence of numerous cystic renal tubules. Such a normal physiological event, however, may be converted into an abnormal or pathological condition if such tubules do not give way at the end of their allotted time, but continue to grow and expand to the detriment of adjacent structures." He goes on to show how isolated renal cysts can easily result from the persistence and expansion of cystic tubules which fail to collapse and finally points out that congenital cystic kidneys where the entire organ is affected, may have their inception in the wide-spread persistence and cystic degeneration of the cystic uriniferous tubules which he has described.

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# Chronic Articular Rheumatism of the Vertebrae Followed By a Progressive Degenerative State of the Spinal Cord\*

BY ALFRED GORDON, M.D., F.A.C.P., *Philadelphia*

CHRONIC articular rheumatism from the anatomical standpoint is invariably of the same character irrespective of its localization, but from the clinical standpoint its manifestations are polymorphous. Particularly interesting is the affection when it is localized in the vertebrae and especially in the intervertebral spaces, because in some such cases the course of the manifestations may be so insidious that their evaluation may be overlooked for a long time until gross, serious and incurable symptoms referable to the spinal cord via the roots become conspicuous. The two cases reported below present a striking illustration of such an occurrence.

*Case 1.*—G. F., middle-aged man, commenced seven years ago to experience a weakness in both legs; more in the right than in the left. The condition gradually increased so that he had difficulty in walking. At no time did he suffer pain or have any subjective sensory disturbances, beside a sensation of heaviness. He came under my observation about three months ago and the following condition was revealed. In walking he frequently stumbles, especially with the right foot. Going down or up stairs or getting up a curb on the street, or walking in the dark the patient experiences considerable difficulty. The toes frequently strike the ground, although there is no marked foot-drop. However, there is some weak-

ness in the extensor muscles of both legs. There is no atrophy of the musculature in the affected extremities. There is no ataxia in gait and station. Romberg sign is absent. Objective sensibility is intact. Resistance against examiner's hand is diminished in every segment of the limbs. The patellar tendon reflexes are greatly increased. Ankle-clonus is absent on both sides. The plantar reflex is frequently extensor by all methods on the right side, but sometimes the toes remain indifferent, but at no time do they flex. On the left side the toes invariably remain indifferent on stimulation of the plantar surface. The abdominal and cremasteric reflexes are abolished on both sides. A detailed examination of the upper limbs, of the pupillary reactions, of ocular muscles, of the fundus oculi, of the sphincters, gave negative results. Wassermann test of the blood and spinal fluid, the colloidal gold reaction, urine, the blood chemistry—have also been negative. The patient experiences great discomfort in the lumbar region in leaning forward or backwards or else in lifting heavy objects. Only occasionally has he pain in the lumbar region radiating down the legs. X-ray examination of the spine revealed a complete obliteration of the intervertebral spaces at the lower levels of the 3rd and 4th lumbar vertebrae, also thickening of the lateral surface of several vertebrae. Such a condition is due to rheumatic deposits.

To sum up, we are dealing with a case of chronic rheumatism of the spinal column

\*Patients exhibited at the February Meeting of Philadelphia Neurological Society.

in which gradually and imperceptibly disturbances referable to the motor tract of the cord made their appearance without affecting the sensory tracts. The diagnosis is therefore "Subacute degeneration of the motor pathway of the spinal cord as a consequence of a rheumatic obliteration of the intervertebral spaces."

*Case 11.*—M. L., 56 years of age, began to notice the present disorder about 10 years ago. At that time he commenced to have

an elevation. Walking in the dark is hazardous, as the patient feels insecure. Lately a weakness appeared in the right arm and hand, also occasional spasmodic contractions similar to those of the lower extremities. There is no ataxia in station or gait, but there is a certain amount of dragging in the right leg. There are no objective sensory disturbances in any of the four extremities. Patient complains of heaviness in the legs and of great discomfort in the



FIG. v.—Case I. X-ray picture of rheumatic changes in lumbar vertebrae.

some discomfort in the lumbo-sacral region. Soon involuntary spasmodic contractions appeared in the right leg. They would appear in walking or standing. Weakness soon developed in both legs, more in the right than in the left. This paretic condition progressed very slowly, but the spasmodic contractions gradually decreased.

At present the resistance of the muscles in the lower extremities is very slight, as it can be easily overcome, with predominance on the right side. There is awkwardness in walking and in going up and down

lower back. There is no atrophy of the musculature of the limbs. The patellar tendon reflexes are exaggerated on both sides, more on the right than on the left. There is a slight ankle-clonus on the right side. The plantar reflex is present in extension on right and indifferent on the left side. The abdominal reflex is diminished and the cremasteric reflex is abolished on the right side. The sphincters are intact. Examination of the eyes gave no abnormal findings. The Wassermann reaction of the blood and spinal fluid, also the colloidal

gold reactions—are all negative on repeated tests. Urinalysis is negative. Blood count and blood chemistry are all normal. Because of the persistent discomfort in the lower back an x-ray examination of the entire spine was made and it shows a chronic osteo-arthritis of the lumbar spine, also a sacro-iliac synchondrosis.

To sum up, the second case presents a chronic rheumatic state of the lumbar spine

nevertheless spasticity which is to be expected by the nature of the localization of the disorder is totally absent. On the other hand there is no genuine flaccidity, the legs move slowly and heavily and the resistance can be overcome. The two cases are not examples of a well-developed typical Spastic



FIG. 2.—Case II. X-ray picture showing chronic osteo-arthritis of lumbar spine.

of 10 years' duration, during which period motor phenomena very insidiously developed indicating an invasion of the motor tract of the spinal cord.

The two cases herein reported are examples of exclusive motor tract involvement which chronologically followed an onset of a rheumatic condition of the vertebrae. The striking feature in them lies in the fact that while all the symptoms indicate a condition found in primary lateral sclerosis.

Paraplegia which pathologically is characterized by a total degeneration of the pyramidal tracts. In our cases we have all the other evidences of an invasion of the same tract except spasticity of the limbs. Moreover, in spite of the duration of the disease (10 and 7 years respectively) it has not reached the degree of motor degeneration which is found in typical Primary Lateral Sclerosis. One is therefore led to

conclude that in both affections the seat of the morbid process is identical but the degenerative process is probably different. Spasticity is characteristic of Spastic Paraplegia, while it is absent in our two cases in spite of the fact that all other manifestations are indicative of a lesion in the same pathway.

An analogous condition we find, when we attempt to differentiate the classical system diseases of the spinal cord from the degenerative changes in the cord associated with severe anemia. In both cases there are symptoms of involvement of the posterior and lateral columns, but certain symptoms may be pronounced in one, not in the other. For example, in some cases ataxia may be accompanied by spasticity of the extremities, in other cases there may be ataxia and hypotonia of the limbs. In still other cases the disease commences with ataxia and spasticity and then later the spasticity disappears and flaccidity makes its appearance. In the affection due to anemia the onset is usually extremely slow and not infrequently spasmodic contractions of the involved muscles occur. Finally in the same disease the motor impotency never affects the upper extremities to the same extent and intensity as in the lower extremities, even in the most advanced stages of the disease. A strikingly analogous clinical condition is found in the two cases described above, with this difference that in them the lesion is confined to the motor tract alone, while in the anemia cases, the lesion is in postero-lateral tract. The first as well as the latest writers on this subject considered the syndrome as a subacute degeneration and sclerosis of the postero-

lateral tract of the spinal cord in contradistinction to the classical system-disease known as posterolateral sclerosis. In corroboration of their clinical contention they called attention also to the pathological differentiation. They found as characteristic the absence of shrinkage which is ordinarily found in the classical system disease, also the fact that the pathological lesion advances by gradual formation and subsequent coalescence of small foci. The existence therefore of a subacute form of combined sclerosis is authoritatively recognized (Dérèjine, Claude, Shaeffer, etc.)

The same consideration is applicable to the cases which present analogous clinical features in involvement of the motor pathway to the exclusion of any other system of fibers. It was mentioned above that the two cases described in this essay resemble and differ at the same time from the classical spastic paraplegia. They demonstrate the existence of a *subacute form* of primary lateral sclerosis. The course of the disease, the character of the symptoms are not all those of the classical primary lateral sclerosis and still the evidences are in favor of the pyramidal tract involvement. The development of the symptoms indicates that there is a considerable integrity of a large portion of the motor tract because of the absence of rigidity, and yet the lesion is sufficiently irritating to produce the increased knee-jerk and the extensor type of the plantar reflex analogous to those found in the subacute degeneration of the postero-lateral columns mentioned above or of the posterior columns (Marie, Crouzon and Dérèjine.) The literature on

subacute degeneration of one single tract in the cord is extremely meager. Two cases of that type were described by me in the *Archives of Diagnosis* 1921-1922, p. 131.

#### CONCLUSION

The interest of the present contribution lies not only in a special variety of affections of the spinal cord, but also and particularly so, in the occurrence of a condition which may be overlooked in the early phases of its development. When in the absence of traumatism or of a toxic-infectious state, of else of anemia, an individual gradually and progressively develops a weakness in the extremities, with or even without muscular atrophy, difficulty in station or gait, slight but distinct changes in the tendon or cutaneous reflexes, in all such cases a pathological state of the vertebrae or of the intervertebral spaces should be suspected. Radiographic examinations are then essential. Not infrequently vertebral rheumatism of a chronic character will be found. Osteophytic formations, nodules of various shape and form will be observed, obliteration of the intervertebral spaces, osteoporosis in the form of bright spots will be seen. It is true that in such cases there is frequently pain in the spine or in the gross articulations of the limbs before motor disturbances make their appearance. Chronic rheumatism is frequently a very painful affection. However, it would be a gross error to believe that this is always the case and that without pain there cannot be chronic rheumatism. Radiographic studies have shown that in many individuals who never or very slightly

suffered, there were osseous lesions such as proliferation and rarefaction (Heberden's or Bouchard's nodules) which are ordinarily considered as characteristic of chronic rheumatism and which are identical with those found in rheumatism of long duration. This observation is correct with regard to rheumatism not only of gross and small articulations in the extremities, but also in the vertebrae or any other bony localization. It is therefore evident that in all cases of an oncoming weakness or of fully developed paresis of limbs with or without any atrophy, the cause of which is unknown or not manifest, radiographic studies of the bony structures and especially of the spinal column are indispensable. In this respect the extensive observations of André Lèri, particularly those which are concerned with the brachial plexus in chronic cervical rheumatism deserve special mention (*Journal Médical Français*, 1924, V. XIII; p. 273.) As to the pathological mechanism of disturbances in the extremities in cases of vertebral rheumatism, it is to be presumed that there is a radiculitis of an inflammatory or compressive character. Pain of course is always present to a greater or lesser degree, but it is not constant or permanent. Muscular atrophy is another manifestation which is frequent. A parietic condition is inevitable. Disturbances of objective sensibility of radicular distribution is to be expected. All these symptoms are the result of the passage of the roots composed of motor and sensory nerve fibers through the intervertebral foramina which are either inflamed or narrowed by the chronic rheumatism. A priori, such a clinical picture is to



be expected in every case of vertebral rheumatism. In reality, however, we have great varieties. In some cases the motor symptoms predominate, in others the sensory manifestations are conspicuous. In advanced cases there are evidences not only of involvement of the nerve trunks of the limbs, but also of the sensory or motor pathways in the spinal cord and of the cells of the anterior horns. There are also variations in the cause, duration, and rapidity of degeneration in the white matter of the cord. The affection described under the name of spondylose rhizomélique is another variety of the condition under discussion. Bechterew called attention to a limited kyphosis with ankylosis localized in the upper portion of the spine without involvement of the limbs. Strümpell under the name of "chronische ankylosierende Entzündung der Wirbelsäule" and Marie under the name of "spondylose rhizomélique" described a pathological condition of the spine with involvement

of the limbs. Both types belong to the domain of polyarthritides deformans of the spine with secondary invasion of the roots, meninges and tracts in the spinal cord. Many intermediary forms belonging partly to one or the other of these types have also been described. The two cases presented above as well as those of the previous contribution (loc. cit.) are examples illustrating the variability in the localization of the lesion within the spinal canal and cord. They are also illustrative of the not infrequent existence of "*rheumatic root affections*," of the importance of radiographic studies of the vertebral column and of the valuable assistance of the latter in our endeavor to determine the causative lesions in cases of an apparently mysterious and progressive motor paralysis. The suggestive features concerning the special variety of systemic disease of the cord in these cases have been already emphasized on the previous pages.

# A Fatality Following the Intravenous Use of Ammonium Ortho-Iodoxy Benzoate\*

BY BERNARD A. MANACE, M.B. (TOR.), *Ann Arbor, Michigan*

AMMONIUM ortho-iodoxy benzoate has been introduced recently by Young and Youmans' (1) for the treatment of arthritis, and these authors have reported favorable results in patients presenting the chronic infectious and hypertrophic forms of the disease. It is closely related in chemical structure to the salicylates and has been extensively investigated in order to determine its physiological action. Since its introduction in the therapy of arthritis, a little over three years ago, Smith (2) has investigated the use of the drug in the treatment of arthritis and emphasizes the similarity of its action to that of the salicylates. Although he obtained quite severe reactions, particularly following the intravenous route, no serious sequelae followed. More recently, Trauba (3) and Cottrell (4) have carried out similar investigations and report favorable results in the treatment of arthritis.

The purpose of this case report is to indicate that the intravenous administration of ammonium ortho-iodoxy benzoate is not without danger. I have had occasion to give the drug to a limited number of patients on the wards of the University Hospital. One hundred cubic centimeters of a one per cent aqueous solution of the drug were injected slowly into an arm vein.

Invariably, the patients have had a more or less severe reaction, beginning usually after forty to fifty cubic centimeters had been administered. Patients would experience occasionally a burning sensation along the course of the vein, but the usual reaction was a severe burning in the eyes with lachrymation, smarting in the nose and tongue, and a sensation of tingling all over the body. Not infrequently chilliness or even a chill, with slight rise in temperature was experienced following the injection. Nausea and anorexia were frequently observed in addition. The unpleasant symptoms disappeared in fifteen or twenty minutes, and invariably the patient would feel better, although in many instances there was no appreciable change in the signs and symptoms of the arthritis. Venous thrombosis near the point of injection occurred in a few cases and sometimes extended along the full length of the arm, even involving a side branch of the vein.

## CASE REPORT

The patient, a single woman of fifty-seven years, weighing about ninety pounds, was admitted to the Medical

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Ward on September 2, 1927 complaining of swelling and pain in the joints, and presenting marked deformities. She had always enjoyed good health, but since the age of twelve years had had a discharging left ear, associated with buzzing, ringing, and impaired hearing. About sixteen months prior to this admission, she first noticed a slight swelling and pain in her ankles, and in a few days she was unable to put on her shoes. Then other joints became involved, chiefly the knees, shoulders, elbows, wrists, and small joints of the hands. By February, 1927, she was unable to stand, and since that date has been confined to her bed and chair. All of the teeth had been extracted without relief.

Physical examination revealed a middle-aged, white female, lying quietly in bed, whose development was fair, but nutrition poor. The skin was pale, and somewhat atrophic. The face was mask-like, full and rounded, with a marked malar flush. The pupils reacted to light and accommodation. Her chest was somewhat deep antero-posteriorly, showed fair expansion, was hyperresonant throughout, and a few fine, moist râles were heard at each base. No apparent abnormality in contour, size, or position of the heart was found. The heart sounds were regular, of good quality and somewhat rapid; no murmurs were heard. Blood pressure was 138/70 and the pulse was regular and forceful with a rate of one hundred per minute. Abdominal examination was essentially negative.

The extremities showed a very marked and advanced arthritis deformans with fixation of the joints in malposition. Both arms were held ad-

ducted to the thorax, with elbows flexed and immobile at an angle of ninety degrees. The hands were flexed at the wrists, with the fingers in extension and deviated to the ulnar side. The position of the hip joints at rest, was flexion at about forty-five degrees onto the torso. Both knees were fixed at a flexion of ninety degrees. The feet had a valgus deformity. Marked muscle atrophy was present in the arms, hands, legs and feet. There was very marked periarticular thickening about all joints, and crepitus could be elicited with passive motion.

The spine showed a marked rigid convexity involving the dorso-lumbar region.

#### COURSE IN THE HOSPITAL

On September 27th, 1927, at 3:00 p.m., the patient was given 100 c. c. of one per cent "Amidoxyl" (ammonium ortho-iodoxy benzoate), using one of the small veins on the dorsum of the hand. The time required for administration was about thirty-five minutes. No apparent reaction followed, even the usual complaints of discomfort being absent. The patient was next seen by the interne at seven p.m., and nothing in particular was noted until about ten p.m. when she complained to the nurse about not feeling well. A few minutes after this she seemed irrational and her pulse became weak and thready. At 10:10 p.m., she quietly expired.

#### POST MORTEM FINDINGS\*

Macroscopically all the blood vessels of the brain (meningeal, basal, choroidal), were considerably engorged. The meninges showed no thickening, or exudate. The brain substance was ede-

matous, and quite soft. No evidence of hemorrhage or thrombosis was found in any portion. The lungs, on cut section, revealed extensive congestion, more so on the right, but no definite pneumonic process was present. The liver and intestinal mucosa were markedly congested.

Microscopically, the above gross central nervous system findings were corroborated. The lungs were the seat of a marked acute exacerbation on a chronic congestion, associated with edema. Many small hemorrhages by diapedesis were noted. Advanced sclerosis involved the aorta, aortic valves and coronaries. The abdominal viscera showed chronic passive congestion.

The cartilages of the knee joint were considerably eroded, being replaced by granulation tissue, with some areas of organized fibrin. A chronic productive perichondritis with periostitis was present. The vertebrae showed osteoporosis with excess fatty marrow and some atrophy.

Examination at the site of injection failed to reveal any thrombosis or inflammation.

#### COMMENT

This is the first fatality which has been reported following the intravenous use of ammonium ortho-iodoxy benzoate. It is an indication that the

drug should be used with discretion. It is well known that some people are sensitive to salicylates, and it is not improbable that patients will exhibit varying degrees of susceptibility to ammonium ortho-iodoxy benzoate. Such a fatality might have been avoided, if the initial dose of the drug had been small, i. e. 0.5 grams. To children and debilitated individuals it would probably be more conservative to give only 0.3 gms. as an initial dose. To those who have a known idiosyncrasy to salicylates, small initial doses should be administered because of the salicylate-like action of the drug. It would seem that subsequent doses should be increased with due caution, as in this patient the degree of symptoms during, and immediately following the injection of the drug, seemed to have no direct relation to its toxic action. This fatality has occurred after several hundred administrations of the drug in this hospital, and for that reason does not contraindicate its use in the presence of evidence for its markedly beneficial action. However, it does serve to demonstrate that size of dose to a given patient should receive due consideration.

\*I am indebted to Doctors A. S. Warthin and N. W. Philpott for the pathologic report.

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# The Embryohormonic Relations of the Suprarenal Cortex to Mesothelial Tissues

BY ROBERT C. MOEHLIG, M.D. *Detroit, Michigan.*

IN a previous communication, it was stated that the pituitary gland secretion has a selective action on mesenchymal tissues (1). The suprarenal cortex as a mesenchymal tissue is influenced by the state of the pituitary gland. In this communication it will be shown that the suprarenal cortex secretion has a selective action on *mesothelial* tissues. From the mesothelium are derived the following tissues

1. Striated muscle.
  - (a) Skeletal.
  - (b) Cardiac.
2. Sex glands, ovary, testis, etc.
3. Pericardium.
4. Pleura.
5. Peritoneum.
6. Serous layer of intestines.

A differentiation of the mesoderm into mesenchyme and mesothelium is not agreed to by all authors, some saying that this differentiation is unnecessary and classifying them under the head of mesoderm. But the clinical differentiation found in suprarenal cortex pathology makes this division preferable for clinical purposes.

The close relationship existing between mesenchyme and mesothelium is shown by the work of Lewis (2) who

says: "The migratory mesenchymal cells in cultures of the embryonic chick heart show all stages of transformation from the bipolar and multipolar reticular cells to the flat mesothelial forms. One can actually observe this change in form. Such mesothelial cells seem to differ from the mesenchymal cells only in form and not in structure, indicating that mesothelium is to be considered not as a tissue differentiated from the mesenchyme but merely as a change or transformation in form."

Clark's (3) experiments also show the close relationship of the mesenchyme and mesothelium. His experiments indicate that mesothelium can be formed from the mesenchyme even in adult life.

Assuming then either that mesenchyme and mesothelium are identical or closely related, it becomes apparent from the previous article that the pituitary would have a controlling action on these mesothelial tissues, even without the intermediary action of the suprarenal cortex. The influence of the pituitary secretion on the sex glands is evident from both clinical and experimental work. Smith's (4) work on the induction of precocious sexual

maturity by pituitary homeotransplants is particularly interesting. Certain it is that primary pathology in the suprarenal cortex produces much greater pathological changes in mesothelial tissues than primary pituitary pathology. From these abundant clinical examples we may assume a selective action of the suprarenal cortex on this differentiated mesoderm, the mesothelium.

Starting with the striated muscle system we find both clinical and experimental evidence of the cortex influence. Biedl's (5) extirpation experiments on the fish species, skates and rays, are very interesting. In this species the suprarenal cortex and medulla are separate. Excision of the cortical tissue produced striking symptoms. These, which began as a rule, seven to eight days after operation, consisted of lessened movements and lifelessness. The spontaneous swimming around in the tanks became decidedly less. Fourteen to eighteen days after operation the muscular asthenia became so pronounced that the fish were unable to swim. They lay practically the whole day in a corner of the tank and took no nourishment. Stimuli failed to produce a reaction. Three weeks after operation they died with general prostration.

Elliott and Tuckett (6) concluded that the cortical portion has a definite relation to the skeletal musculature. They noted that the suprarenals increase with the development of the skeletal muscles, the increase affecting mainly the cortex. They also found that the cortex parallels the weight, whereas the medulla remains stationary. Severe exhaustion is always associated with hemorrhagic dilatation of

the blood spaces in the cortex. In the kitten a movement of fat from the outer to the inner third of the cortex was produced by exhaustion. In a dog that had journeyed thirty miles all cortical cells were found to be vacuolized to a degree only seen in the fat bearing zone of the outer third of the suprarenal cortex.

Bardier and Bonne (7) studying the modifications produced in the structure of the suprarenals by tetanization of the muscles, found that these affected the cortex of the gland, not the medulla. Vincent (8) says that we do not know why the suprarenal cortex removal causes death, but it is possible that this is due to some defect in muscular metabolism.

Bauer (9) in discussing Biedl's experiments above quoted, says that the constancy with which cortical extirpation produces muscular asthenia in fishes and frogs up to the highest vertebrates, (Kahn's experiments on apes) points to a fundamental and vital function of the suprarenal cortex for muscle integrity. He goes on to say that animals and rats in particular who have accessory suprarenals and therefore are able to withstand bilateral suprarenalectomy without symptoms, show the suprarenal insufficiency first after muscular exercise. They fatigue easily, and may die suddenly (Albanese 9b, Mauerhofer, 9c.) Analogies occur in human pathology. Epinephrine cannot overcome this muscular asthenia.

Abelous and Langlois (9d) advance the view as does Vincent (8) that the suprarenal cortex neutralizes certain poisonous *muscular* products. Injections of suprarenal cortex extract fail to influence the muscular asthenia but

Bauer (9) says the reason is not to be referred to failure of simple neutralization of poisonous products by cortical substance but that we are dealing with a more complex phenomenon.

Hoskins (10) found that suprarenal extirpation often induces adynamia of from two weeks to permanent duration. Ergographic studies showed reduction of work capacity of individual muscles to one-sixteenth normal. Glycerine extracts of suprarenal glands (whole or cortex only), by mouth or subcutaneously, had no beneficial influence of voluntary activity. Bauer's remarks concerning these failures also applies here.

As reported elsewhere (11) in a series of cases in which suprarenal cortex medication was tried, viz. amenorrhea, muscular asthenia and one case of Addison's disease, I gave five hundred injections of a suprarenal preparation. The results were entirely negative. In this same series of cases I fed over a thousand five grain capsules of desiccated suprarenal substance. Beef suprarenal glands were cut in half and the cortex and medulla were grossly dissected from one another. The cortical portion was desiccated and prepared in the usual manner. Here, too, the results were entirely negative. It follows that with these methods suprarenal cortex medication is without effect.

Moore and Purinton (12) found marked asthenia in cats after removal of suprarenals.

Hartman (13) believes that it is generally accepted that the characteristic symptom in suprarenal insufficiency is muscular asthenia. Strehl

and Weiss (14) observed that cats which were wild became very apathetic after suprarenalectomy.

Juice expressed from the muscles of suprarenalectomized rats when injected into other suprarenalectomized rats produces almost fatal muscular asthenia but has no influence on normal rats (Erni 9e). Erni (9e) found poisonous products in the muscles of suprarenalectomized dogs which were absent in normal animals. According to Elliott (15) the striped skeletal muscle is continuously under a tonic influence possibly in part derived from nerve impulses; but such a condition as myasthenia gravis proves that the tone is not altogether supplied from the central nervous system. He ascribes this tonic influence to the suprarenal cortex secretion.

Kühl (16) found that injection of epinephrine-free cortex extracts is sufficient to delay for hours the onset of the two chief symptoms of suprarenal collapse: muscular adynamia and respiratory disturbance. Epinephrine and other organ extracts did not produce this effect, showing that the cortical extract contains a specific internal secretion. Castaldi (17) found that feeding suprarenal cortex of the ox to the very young guinea-pig favors the formation of muscle.

Clinically of course, we are well aware of the outstanding symptom of *muscular asthenia* in Addison's Disease. From what has been shown previously it would seem safe to assume that the muscular asthenia of Addison's disease is cortical in origin. In stating this I am well aware of the experimental work done in regard to

epinephrine as a remedy for muscular asthenia.

Since the cardiac tissue is a specialized skeletal muscle, it likewise shares in the muscular asthenia. At post-mortem the heart is usually atrophic and the myocardial symptoms common in this disease may be assumed to result from cortical damage. The general impression seems to be that because the medulla gives off epinephrine, a blood-pressure raising principle, that in Addison's disease low blood pressure is due to a diseased suprarenal medulla. On the contrary, the evidence points to a loss of cortical tissue as the etiological factor, and even the low blood pressure may be due in part to the muscular asthenia. I do not, of course, belittle the medullary involvement in Addison's disease.

A recent comment in the *J. A. M. A.* (18) states that the suprarenal glands are indispensable to life. "At present the preponderance of evidence favors the suprarenal cortex as the portion of the structure that is responsible for the genesis of the essential factor."

Concerning sex gland hypofunction and hypoplasia, there is much evidence connecting these conditions with the cortex of the suprarenal gland. MacKenzie (19) says "Probably the interrelationship of the suprarenals and the sexual glands has been demonstrated most clearly."

In Addison's disease Kyrle (20) found deficient spermatogenesis and degenerative changes in the interstitial glands. The clinical manifestations of this state in Addison's disease are the impotence, sterility and amenorrhea.

Leupold (21) found a close rela-

tionship existing between the suprarenals and testes. He found that when the suprarenals contain much fat the quantity of fat in the testes is also high. The testes contain less cholesterol than do the suprarenals and when cholesterol diminishes in the testes and the suprarenals it is generally first decreased in the former. He believes this proves that the suprarenals have a "higher" function than the testes.

Podvissotsky (22) and Mulon (22) both called attention to the resemblance of the ovarian cortical cells to the suprarenal cortex. Mulon (22) believes that the corpus luteum of pregnancy is a temporary suprarenal cortex.

Elliott (15) says that there is reason to believe that suprarenal cortical tissue is embedded in the sex gland itself, giving rise to the lutein cells of the ovary or the interstitial cells of the testis. Serdivuklov's (23) experiments showed that there exists a functional interdependence between the suprarenal cortex, the parenchyma of the corpus luteum and the interstitial gland of the ovary.

Hoskins and Hoskins (24) found hypertrophy of the testes and ovaries in white rats who had been fed desiccated suprarenal substance. Vigor of reproduction is reduced by partial suprarenal extirpation. (Vincent (8)).

Suprarenal cortex hypofunction in relation to the other mesothelial tissues such as pericardium, pleura, etc., is of course not so important. I can find no conclusive evidence concerning this. A smooth glistening peritoneum



is occasionally mentioned in Addison's disease but on the whole the serous layers do not receive any prominent notice.

Proceeding to hyperfunction of the suprarenal cortex in its relation to *muscle tissue* and *sex glands*, we find much to support this embryohormonic relationship.

Suprarenal cortical tumors of a hyperfunctionating type in the young produce marked changes in the sex development and skeletal muscle system. Female infants with this type of hypernephroma menstruate, are precocious sexually and are usually muscular and strong. Infant boys have premature development of the genitalia, and are equal in size and strength to boys at the age of fifteen and sixteen years. They are known as "Infant Hercules".

Linser (25) first described tumors of the suprarenal cortex accompanying precocious sexual maturity in children. Bulloch and Sequeira (26) reported further cases and included a study of cases previously reported. Glynn (27), Hoag (28), Collett (29) and recently Gordon and Browder (30) have reviewed the literature and added cases of their own. The case of suprarenal cortex tumor reported by Gordon and Browder (30) showed a "Herculean" build.

Pseudohermaphroditism is frequently associated with hyperplasia of the suprarenal cortex. Marchand (31) who first reported such autopsy findings found colossal hyperplasia of the cortex associated with a large accessory suprarenal.

Jump (32) says that at present we

are justified in believing virilism and hirsutism are caused by increased functioning of the suprarenal cortex, varying in degree and due in some instances to neoplastic growth of the suprarenal cortex.

Riddle (33) believes that it is extremely probable that the suprarenals regularly and greatly enlarge in close relation to the time of liberation of the ova from the ovary.

Schief (34) basing his work on 1,227 autopsies, found that there is a distinct increase in the suprarenal weight with increasing stature and the testes show a parallel increase in weight with an increase in the adult suprarenal. These findings of Schief support the evidence given in the previous communication, that the pituitary gland, influencing the bone development and stature, likewise influences the suprarenal cortex and sex glands.

There is no need to cite further evidence that the suprarenal cortex is related to sex glands for this is accepted by most authors. From what has gone before, an obvious embryohormonic relationship exists between the pituitary gland, the suprarenal cortex, skeletal muscle and sex glands.

#### SUMMARY

The suprarenal cortex secretion has a selective action on mesothelial tissues.

The important mesothelial tissues, sex glands and skeletal muscle are influenced by the state of the suprarenal cortex.

Both the mesenchyma and the allied mesothelium through the suprarenal cortex are influenced by the pituitary gland.

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# Case of Coronary Occlusion With Complete Heart Block

## Interesting Electrocardiographic Findings

By LOUIS H. SIGLER, M.D., *Brooklyn, N. Y.*

THERE are several features in the following case which make it of sufficient interest to be put on record. The correlation between certain of the electrocardiographic findings and the clinical manifestations; the resemblance of such findings to those of experimental production of coronary closure, as reported by some workers; and, their occurrence in a pulseless individual, with heart sounds practically inaudible, are all factors worthy of note.

The case is that of a Hebrew, male, 70 years of age, retired grocer, whose past history is essentially negative, except for "stomach complaints" for the past twenty years, consisting of constipation, occasional "heartburn" and epigastric discomfort. There were no precordial pain, dyspnea, palpitation or other symptoms referable to the heart, at any time. He was always in the habit of walking fast without the slightest discomfort, up to the onset of the present illness. He never smoked nor drank any alcoholics, and his habits were fairly regular.

On January 18th, 1928, while taking a bath, he suddenly collapsed. On

recovering consciousness several minutes later, he complained of a most agonizing pain in the left precordium, radiating to the left shoulder and arm. Associated with the pain there was marked dyspnea, with a sense of impending dissolution. He was pale, and his entire body was covered with a cold perspiration. The condition lasted about eight hours, when he began to feel better and in twenty-four hours the pain practically subsided, leaving him with only a dull ache. Generally he likewise felt at that time well enough to leave his bed, against the advice of his doctor.

He continued to feel well, and was up and about for seven days. He even did some work around the house without any discomfort, except for some dull ache in the precordium.

I was summoned for the first time on January 25th, 1928, at which time he had an attack similar to, but more severe than that of the 18th. The pain at this time was most severe in the right hypochondriac region. On examination I found a male, about seventy years of age, lying in bed in great shock, and suffering with in-

tense, agonizing pain. His entire body was pale and covered with a cold, clammy perspiration. His face had an ashen-gray appearance. His pupils were dilated and responded sluggishly. He had marked arcus senilis and general arteriosclerosis. His lungs showed signs of congestion, and heart percussed out was enlarged to the right and left. The heart sounds were very faintly audible and rate was slow. The rhythm was markedly disturbed and, together with the almost inaudibility of the sounds, the exact rate could not be made out. He was pulseless most of the time, except that now and then a very thin, thread-like pulsation, was felt at the radials. He had marked rigidity and great tenderness in the right upper quadrant of the abdomen, and, as said before, he pointed to that area as the seat of his greatest pain.

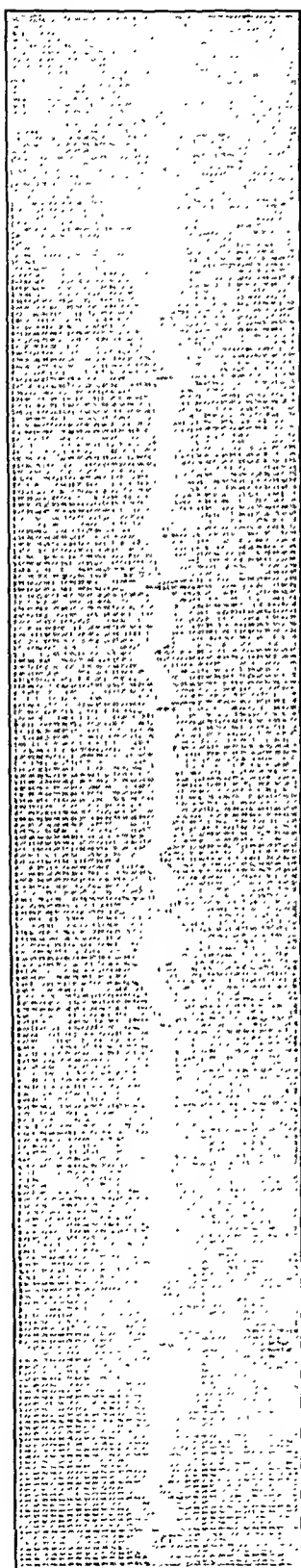
About two hours after the onset of this intense suffering he gradually began to lose consciousness, would doze off for a few minutes, only to be disturbed by the great intensity of pain which would awaken him with a groan. An hour later he lost complete consciousness, assumed Cheyne-Stokes respiration and died in twenty minutes.

The electrocardiographic tracings, taken one half hour before death, show complete auriculo-ventricular dissociation. The auricular rate is about 120 and the ventricular rate, including the aberrant complexes, about 48. The auricular waves seem to be of normal sinus origin, and recur at regular intervals, disfiguring some of the ventricular complexes, marked especially in lead II. The ventricular complexes are of three distinct

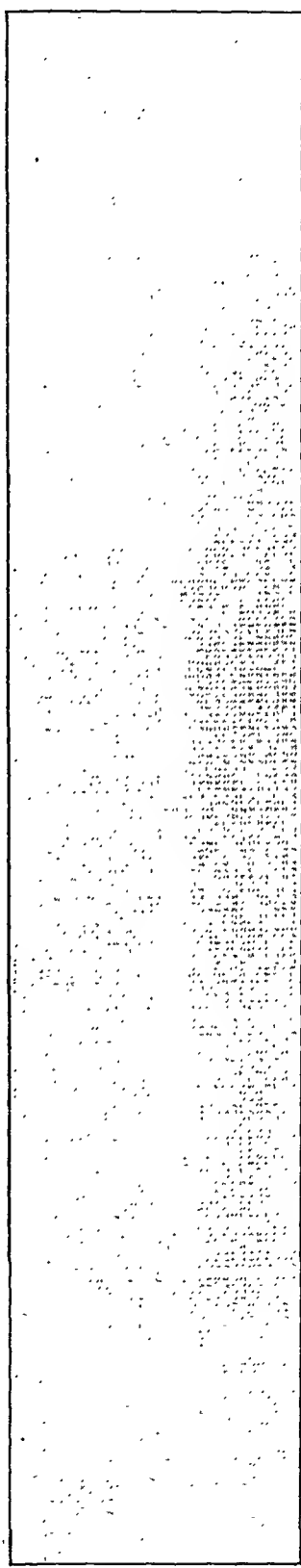
types—a normal supraventricular and two aberrant, originating in two different foci. These assume at times a bigeminal-like character, best seen in lead I (a). At other times, groups of three or more such complexes, starting in the same focus, occur either in regular succession, as seen in lead III, or group themselves in coupling as seen in lead II. There is marked notching in the supraventricular complexes in lead I, and slurring in lead III. The T-wave is interesting. In lead I it is positive, and in the normal complexes it is as high as the R-wave. Its ascent starts from the S-wave and runs directly upwards, not preceded by any iso-electric interval. In leads II and III it is negative. In both leads it starts from the descent of R before it reaches the base line and has a tendency to run somewhat horizontally and downwards before assuming the negative phase, inscribing, in so doing, some curvature. The aberrant complexes seem to have similar T-waves. The complexes are greatly disfigured from time to time by the superimposed P-waves, whenever such waves appear. Both, the supraventricular and aberrant complexes are of low voltage.

#### COMMENT

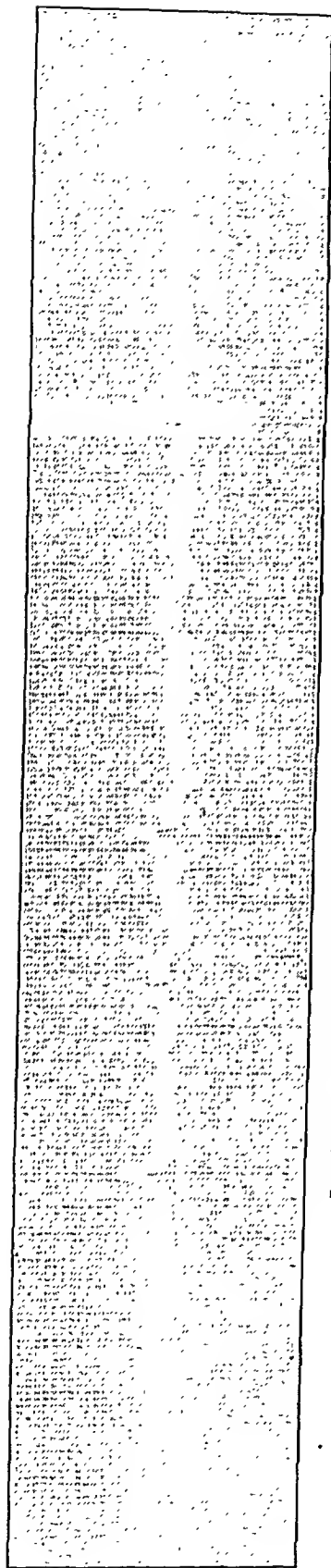
We have here an individual giving no previous history or symptoms of cardiac disease, who suddenly developed an attack presenting a typical picture of coronary closure, followed seven days later by a second, similar but more severe attack. The first attack, although very severe, produced no subsequent symptoms of cardiac decompensation, as shown by his behaviour during the week following the



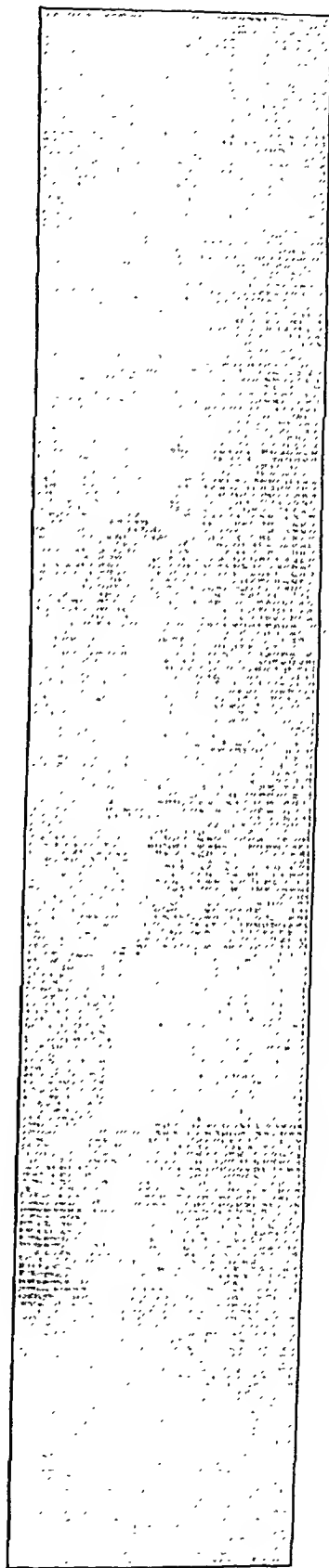
Lead I (a). Deflections—1 millivolt=1 cm. Time—1/5 and 1/25 sec.



Lead I (b). Deflections—1 millivolt=1 cm. Time—1/5 and 1/25 sec.



Lead II. Deflections—1 millivolt=1 cm. Time— $1/5$  and  $1/25$  sec.



Lead III. Deflections—1 millivolt=1 cm. Time— $1/5$  and  $1/25$  sec.

attack. It has, however, made its mark on the myocardium in the form of degenerative changes, as evidenced by the electrocardiographic findings.

The findings telling the tale of the first attack are most probably the complete A-V dissociation and the negative T in leads II and III. In the absence of any evident symptoms of cardiac disease previous to the first attack, it is reasonable to assume that such defects were not present before. That these developed at the second attack is likewise not probable. For, complete block to set in, a certain amount of degeneration of the junctional tissues would be necessary, which would require much more than two hours to develop. Also, the negative T in the two leads is an indication of degenerative myocardial changes of at least one day's standing, conforming with the experimental evidence brought forward by Smith (1). This author ligated various parts of the coronary arteries in dogs, and found a constant change in the T-wave from positive to negative. Soon after ligation this wave was more prominently positive than the normal, which increase in positivity was explained by Pardee (2), quoting the experiments of Eppinger and Rothenberg, as being due to an initial increase in chemical activity following the onset of destruction of tissues. In twenty-four hours the T-wave became negative in one, two or all leads, and the amount of negativity was proportional to the size of the artery ligated, and its supply to the apex. This marked negativity persisted three to four days and gradually became less, so that on the seventh

day, it became again positive in one lead.

Some clinical reports published by Smith (3) later, showed a resemblance of the T-waves in some cases to those of his experimental findings.

Just as the first attack in our case under discussion left its electrocardiographic imprint, so did the second attack. In the latter, we have the premature ventricular contractions occurring singly and in groups, and conforming to the laboratory findings of Lewis (4) and of Smith. Both found, in independent experiments, that within a few minutes to 1½ hours following the ligation of some portions of the coronary arteries, premature contractions set in which in some cases developed into paroxysmal tachycardia. The prematures run in groups of two, three to five or more, and gradually diminish in number after some time.

Although the clinical and electrocardiographic findings in this case harmonize, in the face of experimental evidence, there is a possibility that the latter findings might have been the result of a gradual, degenerative process of many years standing. The presumption that the patient was suffering from myocardial degenerative changes incident to sclerosis of the coronaries with gradual narrowing of their lumina and shutting off of the blood supply to the myocardium, may be true in the face of the usual post mortem findings in such cases. Even in the absence of definite cardiac symptomatology in any case previous to an attack of coronary closure we could not absolutely rule out previous cardiac disease. Subjective symptoms



presented in any history are purely individual, and vary greatly with the susceptibility of the subject. The findings in this case, however, are so strikingly interpretative of occurrences of recent closures, and resemble so closely the experimental data, that we may assume them to be part and parcel of the attacks.

#### SUMMARY

Case report presenting two attacks

with a symptomatology which clinically is interpretive of coronary closure. The electrocardiographic findings, 30 minutes before death, not only confirm the diagnosis but seem to present evidence of each separate closure which occurred at intervals of seven days. The findings also conform with those obtained in the laboratory by various workers.

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## Epilepsy Late in Life

By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., *Professor of Therapeutics, Emeritus, Yale University, New Haven, Conn.*

THE paper of Doctors Riesman and Fitz-Hugh, Jr. on epilepsy in the *Annals of Internal Medicine* for November, 1927, deserves more than a passive reading. This important subject has not been sufficiently discussed, and we are indebted to these clinicians for so ably presenting it.

Besides such cases as occur from arteriosclerosis and endocrine dysfunction, I believe the majority of these cases are associated with mouth infection. Very few persons after forty have healthy mouths; most of them are carrying devitalized teeth, crowns, and often bridges, and pyorrhea alveolaris is very common in persons of this age.

If mouth infection plays an important part, as has been shown, in many types of insanity, it could easily have a causative relation to these late epilepsies. Many thyroid disturbances are due to absorption from infections of the mouth, either teeth or tonsils. This is a clinical fact that can be demonstrated by the removal of these mouth infections and the subsequent marked improvement and sometimes cure of this thyroid disturbance. Whenever a thyroid gland is disturbed by mouth infection I believe the parathyroids are always also disturbed; in

fact, many symptoms of thyroid disturbance are really caused by parathyroid disturbances, and I believe that parathyroid disturbance sometimes, if not frequently, plays an important part in epilepsy. Certainly, disturbance of the parathyroids upsets calcium metabolism, and calcium insufficiency is a very positive cause of nervous irritability. Therefore in every case of late epilepsy the mouth should be carefully studied and every source of infection removed.

Also as noted by Riesman and Fitz-Hugh, some of these epileptic patients have glycosuria or a real diabetes, and I have frequently found that in mild glycosuria, in which slight modification of diet would remove the sugar from the urine, that the eradication of alveolar pyorrhea would allow all of these patients to improve. In other words, they could take more liberal diets without glycosuria.

I have occasionally found that epileptic attacks develop in women at the menopause. Such cases belong to the endocrine dysfunction group of Riesman and Fitz-Hugh. In such cases when the endocrine disturbances have been treated from the endocrine standpoint the attacks have been cured. If there is hypertension at the menopause, corpus luteum treatment is fre-

quently successful in reducing the blood pressure. Any infection or other cause of disturbance or growth of the pituitary gland may be a cause of epilepsy, as epileptic attacks are not infrequent in acromegaly.

Serious eyestrain, a cause that has been much ridiculed, can occasionally cause epileptic attacks, and these epileptic attacks may be cured by proper glasses. Sometimes these cases of eyestrain occur at the period when

presbyopia begins to develop. An epilepsy beginning at this age from this cause may be stopped by proper glasses, if the cause is noted and treated early.

We all recognize the peculiar cyclic habit of the nervous system, and similar to asthmatic attacks and periodic headaches, epileptic attacks, once established, may persist, whatever the cause, in spite of proper treatment.

## Editorial

*Second Annual Exhibition of Works  
in the Plastic and Graphic Arts By  
American Physicians Under the  
Auspices of the New York  
Physicians Art Club*

There has just been held in the exhibition rooms of the beautiful new building of the New York Academy of Medicine, the second Annual Exhibit of original works in the plastic and graphic arts by contemporary American physicians. The first one, held last year, was most successful, not only because of the importance of the exhibit from technical and artistic points of view, but because it demonstrated in the first place the existence in the American medical profession of a considerable body of individuals interested practically in the creation of beautiful things. That exhibit aroused great interest throughout the country, as shown by numerous printed notices of it. It served to crystallize scattered and sporadic efforts at artistic expression by medical men in other parts of the country, as was made evident by the fact that during the year several other physicians' art exhibitions were held in other cities, and by the numerous new exhibitors in this year's show. This movement, however, is but a small beginning in bringing to the light this cultural aspect of the medical man's mental and spiritual makeup. As we have written elsewhere the psychology of the medical life, demands in-

tellectual recreations of a release nature, and such release from the depressing facts of daily professional contacts with abnormal life can be found only in the quest of beauty in nature and in creative art. Throughout the country there are numerous practitioners who seek solace in various attempts at creating something they do not possess, but which in the joy of creation offers that necessary and much-desired psychological catharsis. Without this renewal of outlook there is no human mind capable of retaining that equilibrium of mental and spiritual processes essential to happy and successful living. One, therefore, notes with great pleasure and optimism such evidences of medical culture as those seen at the New York Academy of Medicine. The exhibit was arranged by the New York Physicians Art Club, of which Dr. I. S. Hirsch is the President, Dr. H. S. Patterson the Vice-president, Dr. H. A. Bancel the Secretary and Dr. Herman Fischer the Treasurer. It was well-arranged and well-lighted, in the large room on the ground floor to the right of the entrance in the new Academy building on upper Fifth Avenue. The foreword to the catalogue was written by Dr. George D. Stewart, President of the American College of Surgeons. The catalogue listed eighty exhibitors with two hundred and eighty exhibits. These represented many fields in the

plastic and graphic arts: paintings in oil and water color, etchings, wood cuts, book plates, sculpture, wood carving, marquetry, miniatures, book bindings, architecture, lettering, relief map making, etc. This catholicity of expression gave an especial atmosphere of interest to this collection. One got from it what one does not always get from the exhibitions of professional artists. These were real individual expressions of what attracted the artists', the physicians', to be more exact, personality, and for this reason, to a fellow worker in medical science, the exhibit had a living sense of individual personalities. Here, one felt, were men and women doing for fun, and getting a lot of fun out of it, just the things that appealed to them, that they wanted to recreate and as they wanted to. For this reason exhibitions of amateur art are always more refreshing and satisfying than those of the average professional kind where commercial disposal of the product is too often loudly proclaimed and felt. Matters of style, technique and vogue are of less importance here. What matters is what appeals to the artist as beauty, and his effort to reproduce that beauty. Here is one man interested in waterfowl and he recreates their artistic significance to him; another one sees the elusive beauty and mystery of the sea and ships and strives to hold it; others feel the beauty of mountain tops and upland pastures, of trees and flowers, the human form, houses, phases of human life—it matters not just where beauty is seen and caught—what does matter is that these men and women active in a daily professional contact with the ugliness of disease, feel this

beauty, pursue it and attempt to recreate it. This is the highest form of culture. This is the real artists' spirit. Deficient in technique, crude in execution some of these efforts may be, but the spirit of individual expression is the thing that counts. As a matter of fact, it is wonderful how clever most of these efforts are, and how well done. A comparison with professional work leads to no too-condemnatory attitude. The technical methods employed are usually straight forward and simple; there is but little attempt at fooling with abnormal modernistic freakish modes. Still, even this might be done for fun also; but the fact remains that the great majority of these medical artists are primarily concerned with the beauty of nature and the human form, and attempt in the simplest and most honest mode to recreate it. Of the things that appealed especially to the writer may be mentioned "The Lonesome Barn" by John Howard Allen of Portland, "A Landscape" by Frederick Adams of Seattle, "Old Veterans" by Herman Fischer of New York, "Old Bridge" by Leigh H. Hunt of New York, "Texas Blue Bonnets" by Sallie W. Miller of Slaton, Texas, "A Bit of Norway" by J. R. Nilsen of New York, "Hill Pasture" by R. C. Larrabee of Boston, "Olympic Mountains" by F. W. Southworth of New York. These preferences, however, are probably the result of the personal appeal made by the subjects as well as by their successful reproduction. It was characteristic of this exhibit that the great majority of the artists drew their inspiration for creation outside of their professional field. There were few attempts at purely scientific draw-

ing or illustration, or at artistic representation of material from the medical life and professional contact with human life. Not that these do not offer rich fields for artistic expression and creation; but the writer was interested in the fact that appeared very patent to him, that the material chosen for art subjects in this exhibit were true release subjects. Perhaps for the greatest recreative good to the medical man this getting outside of his professional field offers the highest values, if he works only in this one field of recreation. The farther removed from vo-

cational atmospheres, perhaps the greater cultural good for the man of medicine. It is to be hoped that this movement for exhibitions of art works produced by medical men will extend throughout the country, and that interested groups throughout the larger cities, at least, may be incited to concentrate and crystallize this aspect of the medical man's cultural life. Incalculable good to the profession must come out of such efforts, which in the end lead to that most desired result of all—the liberal education of physicians.

## Abstracts

*Physiological Factors in the Genesis of Gallstones.* Fourth Ludvig Hektoen Lecture on the Billings Foundation. By PEYRON ROUS (The Proceedings of the Institute of Medicine of Chicago, April 15, 1928).

Knowledge concerning gallstones is just emerging from the observation stage. Experiment has shown that the calculi developing out of the bile of laboratory animals differ essentially in their constitution from human gallstones. It is the human problem that is important; and it might seem that animal experimentation on gallstones is a waste of time, were it not for the fact that human biliary calculi are to a very large extent the product of physiological activities that can be studied advantageously in animals. These physiological activities are the constants of the gallstone situation as contrasted with the variables such as infection, dietary habits, tight lacing and the like. The variables are subject to alteration as situations and customs alter. But neither endeavor nor whim will enable an individual to go free of his physiological actions and responses. The riddle of cholelithiasis resolves itself into two questions, how stones begin and why they grow. Observation has shown that biliary calculi cannot in general be explained as merely the result of deposition out of a supersaturated bile upon any nucleus that comes to hand. A great variety of formed sediments which might conceivably serve as the beginning of stones is to be found in human gall-bladders, but their effect in this relation is to all intents and purposes nil. For the nucleus of the great majority of human stones would seem to be a very special thing. The majority, or all, of human stones have a pigmented center consisting of calcium bilirubinate. Whence comes this nucleus and under what conditions? It is possible to follow the early development of gallstones

out of the sterile bile of dogs and thus to gain knowledge bearing upon the problem. While dog stones differ from the ordinary run of human stones, being made up almost entirely of calcium carbonate, as seldom happens in man, their nuclei consist of the same material, calcium bilirubinate. This substance does not occur in normal bile despite the presence there of the ingredients necessary to its formation. Day to day study of the dog has shown that when the animal is seriously ill from any one of a number of various causes, bilirubinate often comes down out of the liver bile in the form of minute brown granules. Under such circumstances the granules may appear in veritable showers, and during the weeks that follow, stone formation takes place on them, as it does not, in general, on such other formed sediment as may be present. Only when there are considerable accumulations of cell debris exposed to the bile current does stone formation occur in the absence of bilirubinate nuclei. The gradual development of carbonate stones in the midst of such debris may be thought of as a variant upon the calcification so frequent in dead tissue elsewhere throughout the body. Carbonate stones occasionally arise under similar conditions within the human biliary tract. From the observations on dogs it may be inferred that some intercurrent illness, by bringing about the conditions for a precipitation of calcium bilirubinate from the bile, will act to provide during the lives of most individuals more than sufficient potential nuclei for stone formation. This being the case, it seems amazing that stones do not occur more often under natural conditions. For in comparison with the number of possible nuclei stones are rare. Many kinds of foreign bodies have been introduced into the biliary tract of animals in the attempt to produce

stones, but as a rule without success. Such bodies, like the bilirubinate nuclei, act merely to pull the trigger of calculus formation, but usually the gun is empty. It is in the circumstances surrounding the development of calculi, not in the occurrence of suitable nuclei for them that the real problem of gallstones lies. The simplest possible stone formation would be by deposition from a supercharged bile. Such a deposition is probable in the case of the solitary cholesterol stone of man, and that a diathesis may be responsible for the bile character in some such instances and dietary habits in others. The question has arisen whether pure pigment stones—stones consisting of calcium bilirubinate—are not diathesis stones as well. One can suppose a persistence of the initial derangement which leads to a deposition of calcium bilirubinate nuclei out of the bile has much to do with their formation. In this relation it is worth while to realize that about 60 per cent of patients with congenital hemolytic jaundice show gallstones at autopsy, bilirubinate concretions which have formed out of biles abnormally loaded with pigment, and at an age when cholelithiasis is notably rare. If a supercharged bile will explain the occurrence of a small proportion of human stones, what is responsible for the more frequent ones? Biliary stasis alone is not sufficient, nor stasis and a foreign body, nor even stasis, foreign body and infection are sufficient to produce animal stones, unless the last gave rise to a low grade chronic cholecystitis, and even this last was far from being a regular occurrence. Animal experimentation has sufficed to show, that although human and animal stones differ in constitution, the conditions under which they arise are the same in both. The normal gall-bladder acts to render its contents acid; the more concentrated the bile the more acid, and the less likelihood of stone formation. It might be inferred that if the gall-bladder is prevented from rendering its bile acid, stones will form. There exist in the literature observations strongly suggestive of this. However, no adequate study of the reaction of the biles associated with human stones has been made, and one cannot say whether a functional failure in this relation on the part of

the organ will result in cholelithiasis. The possibility suggests itself that the loss of one function and the retention of another by the organ may have even more baneful consequences than if both are wanting. This question of the immediate cause of gallstones cannot be settled with our present knowledge. Speculation is idle, and the question must be left to future investigation.

*Observations on Urobilinogen in Urine.* By JOHN B. DEVINE AND G. O. BROWN (Proc. for Exper. Biol. and Med., March, 1928, p. 502).

Urobilinogen of the urine was estimated quantitatively by the method of Gerwen. Definite increases in urinary urobilinogen were found in cases of liver pathology. Increased values were also found in some cases of diabetes mellitus, most of which showed some suggestive evidence of an accompanying liver pathology. This was proven in two cases coming to autopsy, one of which showed cirrhosis and the other marked passive congestion of the liver. Increases were also found in some cases in which no definite evidence of liver pathology could be found. Active cases of pernicious anemia showed this finding. Cases of severe nephritis frequently showed increased urinary urobilinogen. It is questionable whether this should be attributed to a possible accompanying liver lesion or to increased renal permeability to this substance. Nephritic cases with a high urobilinogen output are usually accompanied by anemia. A similar high urinary pigment output is noted in other secondary anemias of obscure etiology. This suggests that loss of pigment may play some rôle in the production of the anemia. A few cases of renal glycosuria were found to have high values for urinary urobilinogen. This may also be due to increased renal permeability. The occurrence of increased output of urobilinogen in urine of cases in which no definite evidence of liver pathology could be discovered, impairs the value of the use of this reaction as a test of liver function.

*Carcinoma of the Esophagus.* By EDWARD S. CLAYTON (Surg., Gyn. and Obstet., Jan., 1928, p. 52).



This is a study of 41 cases of esophageal cancer seen in the last 5 years at the Philadelphia General Hospital. The average age of these patients was 60 years and 6 months, and the great majority were in their sixties. 39 were males; 8 occurred in the colored race. Cancer of the esophagus forms a little more than 5 per cent of all cancers. It is a lesion occurring for the most part in males. Symptoms occur very late, the average duration of life after the onset of the first symptoms being about 7 months. The most common symptom causing the patient to seek medical aid is difficulty in swallowing, while dysphagia in its true meaning, painful swallowing, is very common. About 75 per cent of esophageal carcinomas metastasize, and the cause of death most commonly is an intercurrent bronchopneumonia. The lesion occurs most commonly at the level of the bifurcation of the trachea at the point where the esophagus is crossed by the left bronchus. The second most frequent situation is about the point where the esophagus passes through the diaphragm. These are the points where normal anatomical constrictions of the esophagus are most marked except at its beginning. There is no relation between the duration of symptoms or the size of the local lesion and the extent of metastasis, for some of the smallest lesions give rise to extensive metastasis, while, on the other hand, some of the most extensive local lesions give rise to very little, and some to no metastasis. The depth of the esophageal wall involvement does not have any relation to distant metastasis, but does to local extension. The most important factor with the duration of life and the extent of metastasis is the degree of malignancy of the individual growth, which can be determined by the microscopical examination. The position in which the cancer occurs in the esophagus does not have any relation to the extent of metastasis, but does have some relation to the direction of metastasis. Cancers of the upper third metastasize to the glands in the superior mediastinum or deep cervical glands. Those of the middle third commonly involve the lymph glands around the bifurcation of the trachea. They metastasize below the diaphragm less commonly and less

extensively than do those involving the lower third. Cancers of the lower third most commonly metastasize below the diaphragm through the coeliac chain. It seems unlikely that radium will have any place in the treatment of esophageal cancer, for the wall is involved deeply, and in most instances if the cancer cells could alone be picked out, perforation would occur, and the patient die of empyema, abscesses or some chest complication.

*Principal Causes of Illness in Typical American City* (UNITED STATES PUBLIC HEALTH SERVICE, March 26, 1928.)

Public Health in a given community depends upon the personal health of each individual. Health officials generally have recognized, according to Surgeon General Cumming of the United States Public Health Service, that although a great deal is accomplished by means that deal with community conditions, yet the individual is the foundation upon which the public health is built. In order to know what diseases must be guarded against it must first be known what diseases are present.

Not only the causes of death but the causes of ill health as well are of great importance to health officers and physicians in their scientific searching for causes and conditions in their preventive work. Of far greater importance than death rates and life table expression is a view of the health situation depicted by physical impairments as revealed by competent medical examinations and by morbid conditions as ascertained by adequate records of sickness.

With this thought in mind a study was conducted by the Public Health Service extending over more than two years in a city regarded as a typical American small city in one of the eastern States. The information obtained through this study is of great interest to the general public as it shows clearly what diseases are most prevalent in the general population.

The city in which these studies were conducted may be said to be typical of many other cities of its size in the eastern section of the United States. The principal object of this study was a record of illnesses that were experienced by a population group com-

posed of persons of all ages and both sexes, and in no remarkable respect unusual. The records of illnesses obtained were of illnesses as reported to experienced investigators. The reports were made by the household informant, usually the wife, either the sickness as experienced by herself or as she observed it in her family.

The rate of sickness from colds and bronchitis was the highest, being annually 418.6 per 1,000 persons. Influenza and gripe came second with a rate of 143.2 per 1,000; diseases of the digestive system were 96.5 per 1,000; tonsillitis and sore throat 65.7; confinement and other puerperal causes 46.9; diseases of the nervous system, including headaches, 44.1; accidents and other external causes, 39.5; measles 34.2; whooping cough 22.6; rheumatism and lumbago 21.8; heart and other circulatory diseases 18.3. The list contains ten or eleven more items and concludes with hay fever and asthma which is shown to have caused 5.8 cases of sickness each year per 1,000 persons.

From this study fairly accurate records of real illnesses were secured. As a matter of fact less than 5% of the illnesses of exactly stated duration were recorded as one day or less in duration; nearly 80% were three days or longer, and 60% were eight days or longer in duration. Approximately 40% were not only disabling but caused confinement to bed. It is evident, therefore, that in the main the illnesses recorded were more than trivial in their character, in spite of the fact that in some instances mere symptoms were given as diagnoses.

There are certain facts from this study that stand out with particular significance. First, the extraordinary high incidence of sickness shown in early childhood was a rather surprising result. Illness was far more frequent under 10 years of age than at any other time of life. Second, the interesting suggestion was afforded that the average individual is more free from illness in the age period 15 to 24 years. Thereafter sickness becomes more frequent as age advances, and it may be added, upon the basis of other studies as well as these, that sickness becomes more severe and more frequently fatal.

The picture given by the record of sick-

ness according to causes, or more precisely, according to the kind of sickness is in sharp contrast to that given by causes of death. Respiratory diseases and disorders account for 60 per cent of sickness as against 20 per cent of deaths. The general group of "epidemic, endemic, and infectious" diseases account for eight per cent of illness, whereas only about 2 per cent of the deaths were due to this group. Digestive diseases and disorders caused 10 per cent of the illness as against 6 per cent of the total deaths. On the other hand, the group of general diseases (which includes cancer, the diseases of the nervous and circulatory systems and the diseases of the kidney and related organs) were relatively much more important causes of death than of sickness. The diseases of the heart and blood vessels show the sharpest contrast—24 per cent of deaths are due to these conditions, as against only 2 per cent of the sicknesses. In other words, these diseases manifest themselves relatively rarely in definite attacks of sickness, although they undoubtedly shorten life and make life much less enjoyable while they last.

The prevalence of "chronic" conditions as ascertained by this study is of interest. Of each 1,000 individuals on the average 34 were affected with arthritis, lumbago and myalgia; 22 with neuralgia, neuritis and sciatica; 21 with diseases of the heart; 10 with chronic indigestion and other intestinal disorders; 10 with appendicitis; and 7 with nephritis.

The further query suggests itself—at what age is the individual least able to withstand diseases after he has been attacked? One way to measure this is to compare the attack, the greatest resistance to death in childhood being the age period 5 to 14. The lowest resistance is in infancy and early childhood, 0 to 4 years, and in middle and old age. Ability to survive illness thus varies markedly from resistance to illnesses at different ages, particularly in childhood, (5 to 14) when the average individual suffers from illnesses frequently, but has a relatively small chance of dying, and in the older years when not only does his susceptibility to illness increase, but also his chance of death. This is due partly, of course, to the

nature of the illness occurring at these ages, and partly to the diminished ability to resist the diseases which manifest themselves in sickness.

It is believed that one of the most important lessons to be drawn from this study is that public health has as yet barely touched the task of preventing the conditions which manifest themselves in physical and mental impairments, in inefficiency and illness, and in postponable death. Plague and pestilences have been diminished, in-

fant and child mortality from infectious and intestinal disorders, and healthful living is being established more and more firmly as a popular ideal, but aside from these the prevention of disease remains as an outstanding problem yet to be solved.

The hope of the future lies in the continued and increasing growth of scientific knowledge which can be applied to the protection against disease, and the promotion of the public health.

## Reviews

*International Clinics.* A Quarterly of Illustrated Lectures and Especially Prepared Original Articles on Treatment, Medicine, Surgery, Neurology, Pediatrics, Obstetrics, Gynecology, Orthopedies, Pathology, Dermatology, Ophthalmology, Otolaryngology, Rhinology, Laryngology, Hygiene, and Other Topics of Interest to Students and Practitioners. By Leading Members of the Medical Profession Throughout the World. Edited by HENRY W. CATTELL, A.M., M.D., Philadelphia, Volume I, Thirty-eighth Series, 1928. 307 pages, three colored plates and numerous figures. J. B. Lippincott Company, Philadelphia and London, 1928. Price in cloth, \$3.75.

The contributors to this volume comprise L. F. Barker, Herbert A. Black, H. W. Cattell, F. J. Cleminson, Ralph Colp, George G. Davis, John B. Deaver, Leonard S. Dudgeon, J. Epstein, Harold Ernberg, J. H. Garberson, P. N. Hansen, W. F. Harriman, C. W. Henney, E. L. Jones, E. S. Judd, K. H. Krabbe, P. Noubecourt, F. Norsk, W. J. O'Donovan, J. R. Oliver, H. J. Panner, C. V. Patrick, John Phillips, W. D. Reid, Georg Schaltenberg, Victor Schmieden, James Strandberg, Alb. Tillisch, A. Westergren and A. Whittaker. Under Diagnosis and Treatment there are nine articles, dealing respectively with Visceroptosis, Light Treatment, Vertebra Plana, Sanoehrysin, Tularemia, Syphilis, Red Cell Sedimentation Reaction, Human Motility, and Polymucositis. Under Medicine there are three articles: Coincident Intestinal Amebiasis and Syphilis, Chronic Epidemic Encephalitis and Bacterial Heart Disease. Under Pediatrics there are two papers, one on the Clinical Teaching of Pediatrics at Paris, and the other on the Saehska Children's Hospital at Stockholm. In the section on surgery the following subjects are discussed: Uterine Fibroids, Operations and Demonstrations at

the Chirurgische Universitäts Klinik in Frankfurt-am-Main, Surgical Demonstrations at the Kommune hospital of Copenhagen, Otogenous Cerebral Abscess, and Surgical Treatment of Goiter. Under Traumatic Surgery there are presented: Ball Splint for Hand Fractures, Fractures of the Long Bones and Use of Pedicle Grafts in Traumatic Surgery. Two articles are given to Otolaryngology: Tonsillectomy by Use of an Electrically Lighted Mouth Gag and The Otolaryngological Clinic of the Middlesex Hospital. The single paper under Ophthalmology deals with Disturbances of the Autonomic Nervous System by Eye Stress. Under Pathology one article describes specimens of Fetus Papyraceus, Premature Separation of Placenta and Rupture of Uterus. The other article gives the technique of a New Method for the Rapid Microscopical Diagnosis of Tumors. The 1927 Mütter Lecture of the College of Physicians of Philadelphia by E. S. Judd on The Pathogenesis of Gastric and Duodenal Uleers follows. Under Medical History J. R. Oliver presents an interesting and readable paper on The Renaissance. A few medical questionnaires come next and the volume closes with a review of the Progress of Medicine During 1927 by the editor, H. W. Cattell. This volume equals in value its predecessors; there are some good and interesting papers presented, while others have no other value than as padding. As in other volumes the articles written by foreigners are very elementary, and some of them hardly worth the printing. Strandberg's article on the Change in the Clinical Picture of Syphilis is an exception and well worth the reading. The surgical articles are on the whole of more practical value than those under the other headings. Reviews of annual progress in medicine are usually unsatisfactory because of inadequate surveys

of the current literature and lack of recourse to original articles. In spite of its defects the present volume contains enough valuable material as to make its perusal worth the while.

*First Aid and Medical Service in Industry.* A Survey Conducted by DR. H. L. DAIELL. Published by Johnson and Johnson, New Brunswick, N. J. 136 pages, numerous illustrations. Distributed free of cost to any physician interested in first aid and medical service in industry.

The book is a condensation of a special survey of a number of typical industries in the United States. It was made to ascertain the methods employed and the service rendered to employees in the treatment of injuries following the preliminary measures of first aid. The survey included the equipment of first aid rooms, dispensaries and emergency hospitals, inoculation service, physical examination, welfare work, first aid by the layman, etc. Reports of over seventy industries are given, showing those employing from 5,000 to 100,000 operatives, with full detail as to the service, with illustrations of dispensaries, operating and examination rooms. The book also contains specimens of hospital and accident report forms and records of physical examination, with an addenda of miscellaneous contributions. In the reports of specific industries surveyed, only certain types have been selected and only salient points included. The work, it is believed, is the first attempt at such a survey of so important a field. The review has been published at the request of many workers in the field. Much valuable information is contained in this little volume, indispensable to medical men engaged in this line of work.

*How to Make the Periodic Health Examination.* A Manual of Procedure. By EUGENE LYMAN FISK, M.D., Medical Director, Life Extension Institute; and J. RAMSER CRANFORD, M.D., Assistant Medical Director, Life Extension Institute. Foreword by Major General Merritte W. Ireland, Surgeon General, U. S. Army. 393 pages, 81 figures and charts, bibliography. The

MacMillan Company, New York, 1928. Price, \$4.00.

This book is dedicated to the memory of Horace Dobell, M.D., (1828-1917) in whose writings sixty-five years ago appeared the first reference in medical literature to the periodic health examination. In his "Lectures on the Germs and Vestiges of Disease and on the Prevention of the Invasion and Fatality of Disease by Periodical Examinations," London, 1861, Dobell said "I wish, then, to propose as the only means by which to reach the evil and to obtain the good, that there should be instituted, as a custom, a system of periodical examination, to which all persons should submit themselves, and to which they should submit their children." The idea urged unsuccessfully by Dobell is now reaching fulfillment. There is a wide-spread and constantly increasing interest in the periodic health examination movement. It is receiving attention, not only from voluntary health organizations, industrial concerns and insurance companies, but also from hospitals, clinics, individual physicians and the public generally. The National Health Council, which includes in its membership such important organizations as the American Public Health Association, the National Tuberculosis Association, and the United Public Health Service, some time ago sent out a nation-wide appeal for a physical examination for everybody at least once a year. The American Medical Association has requested the physicians of the country to equip themselves to render this examination service and the idea is being taken up in earnest by state and county medical bodies. However, the institutions and physicians now specializing in health examinations cannot hope to accomplish the task before them without the aid of reinforcements. It is evident that the great bulk of the work must ultimately fall upon the general profession. The physician must be trained to the proper conduct of this specialized type of medical work, and for this training there is need of a practical manual of procedure. In February, 1925, a small manual for this purpose was put out by the authors, with the assistance of a special committee of the medical staff of the Life Extension Insti-

tute. Before that time there was no definite standardized outline of procedure available to physicians conducting periodic health examinations covering in an intensive way each region of the body. For more than two years the original manual has been used by physicians at the head and branch offices of the Institute, and it has furnished the groundwork for this more comprehensive volume. It is hoped that this volume will fill the need for a practical manual of procedure to serve as a guide to the physician in the conduct of this specialized type of medical work. The chief merit of the manual may be said to lie in the fact that it represents the consensus of judgment of physicians dealing with the practical problems involved in the conduct of the periodic health examination service, covering a thirteen-year experience and the examination of more than five hundred thousand lives. In the preparation of the volume reference has been made to the best scientific literature available in checking up the material presented. Introductions to the various sections have been written by George C. Andrews, A. Bassler, Lawrason Brown, Louis Casamajor, C. A. Drake, A. C. Fones, E. L. Keyes, J. M. Lynch, Edward Martin, John McCoy, R. T. McKenzie, J. O. Polak, M. P. Ravenel, S. C. Smith, R. T. Taylor and W. Finne. These aid in giving the physician a true perspective as to the importance in a general physical examination of thorough attention to every region of the body. The general arrangement of the volume is: Introduction; Preliminary Procedure; Regional Examination; Laboratory Methods and Standards; Counselling; Essential Points to Cover in Reporting to Examiner; Appendix and Bibliography. The specimen forms and reports included in the Appendix are presented for their suggestive value to the general practitioner who desires to establish a satisfactory office system and to conduct this type of service on a high plane of efficiency. The material presented in this book is all of it of the greatest value to the general practitioner, and it can be utilized by him in acquiring thorough methods of general and special regional examinations. It would be of great value to the medical student and interne as a guide to the ac-

quiring of good and thorough habits of examination. The volume is well written and well printed. It can be recommended as serving its purpose most excellently.

*The Young Man and Medicine.* By LEWELLYS F. BARKER, M.D., LL.D., Professor Emeritus of Medicine, Johns Hopkins University. Vocational Series, Edited by E. Hershey Sneath, Ph.D., LL.D., Yale University. 202 pages. The MacMillan Company, New York, 1928. Price in cloth, \$2.50.

This is one of the vocational series designed to help young men about to make that most important decision—the choice of one's life-work. In spite of the important issues involved in a man's vocational career, little has been done in a practical or systematic way to help our college young men to a wise decision in such a determination. The struggles of the average college student in his efforts to settle this important question for himself, the perplexities, embarrassment and apparent helplessness are pathetic. This is largely due to his ignorance of the nature of the professions and other vocations which appeal most strongly to the college man. Consequently, he does not know how to estimate his fitness for them. He cannot advise advantageously with either his father or his instructor, for both of these are familiar only with the one profession each is following. For this reason a series of books dealing with the leading vocations and prepared by men of large ability and experience, capable of giving wise counsel is a desideratum. Such men are competent to explain the nature of the profession and other vocations which they represent, the personal and educational qualifications necessary for a successful pursuit of the same, the advantages and disadvantages, the difficulties and temptations, the opportunities and ideals; thus, in an adequate way, enabling the student to estimate his own fitness for them. They are also able to make valuable suggestions relating to the man's work after he enters upon his vocation. This vocational series will consist of twelve books written by representatives of the following vocations: Law, ministry, teaching, medicine, journalism,

banking, business, mechanical engineering, electrical and civil engineering, farming and government service. Barker has accomplished a very good service in his presentation of the medical vocation. The first chapter discusses the decision regarding a life career; the second, the services renderable by the medical profession in our social organization; the third, the personal rewards and satisfactions of medical workers, and the appendix is concerned with the educational considerations of medicine. The subject matter is presented in a sane and conservative manner, giving all sides of the medical calling fairly, without sentimentality

or exaggeration. Here is no propaganda for medical training, but a dispassionate description of the medical life in its many aspects, perhaps a little too restrained at times to the older physician who reads it, and who is tempted to greater show of enthusiasm about his own profession. Better, however, that the young man's choice should be founded upon a conservative presentation than upon an over-zealous enthusiasm. The book is very readable, the facts are solid, and are logically presented. We particularly recommend it, as we do the entire vocational series, for a prominent place in the shelves of every High School library.

# College News Notes

1928-29

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The program of the New Orleans Clinical Session of The College seems to be unanimously voted the best and most interesting in the history of the organization. It has been the constant effort of this office, of the Officers and Regents and of the General Chairman to benefit by each year's experience in improving each succeeding Session, and we shall appreciate your comments and suggestions for further improvement.

The next meeting place cannot be selected until the next Regents' Meeting in May or June. Meantime, we should appreciate an expression from you as to your preference for the next meeting place. The following places have been suggested: Rochester, Minn.; Baltimore, Md.; Philadelphia, Pa.; Minneapolis-St. Paul, Minn.; Montreal, Que.

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Other suggestions may also be made.

By direction of the President, the spring meeting of the Board of Regents of The College will be held in Washington on April 29, 2:00 P.M., prior to the meeting of the Association of American Physicians. The meeting will be held in the District of Columbia Medical Society Building, 1718 M Street. (Please note the address and the hour.)

Among matters to be considered at that time are: Reports of the new Committee on Standards of Admission, Committee on Credentials, and the Finance Committee. The personnel of these new Committees, appointed in accordance with the Minutes of the last Regents' Meeting at New Orleans, are given above.

## POST-CLINICAL CRUISE OF THE COLLEGE

The New Orleans Clinical Session in addition to being one of the most successful and profitable meetings ever held, especially in the field of tropical and semi-tropical medicine, was also a very fitting introduction to the Caribbean Cruise, March 10 to 27, to Havana, Cristobal, Colon, Canal Zone, Panama and Spanish Honduras. In fact some of the leading speakers on the New Orleans program, Dr. Aristides Agramonte of Havana, and Dr. William James of Panama, accompanied the party on their southward trip and provided further instruction and entertainment both en route and in their home communities. This afforded an insight into local conditions otherwise unobtainable, and proved once more the medical profession as the greatest fraternity in the world.

The personnel of the party was headed by both the retiring president, Dr. Frank Smithies of Chicago, and the present president, Dr. Charles F. Martin of Montreal, and the executive secretary of the College, Mr. E. R. Loveland of Philadelphia. Other physicians with members of families and friends comprised a party of about forty. The commodious S. S. Cartago of the Great White Fleet (United Fruit Company) was our pleasant and hospitable home throughout the trip, except for one night at the Hotel Tivoli in Panama.

Havana was the first stop. A bright clear morning sun illumined the beautiful harbor, the historic Morro Castle, the Maine monument and the colorful Prado and Ocean drive of the newer section of the City. Dr. Rainold was making his first return thirty years after his service in the medical corps of the Army during the Spanish American War, when he witnessed the surrender of General Weyler and the beginnings of sanitation under Gen. Leonard Wood. The contrast today in general cleanliness and healthfulness was most striking. A general sightseeing tour of the city covered such things as the beautiful University of Havana, the cathedral which once housed the remains of Christopher Columbus, the headquarters of the Cuban Congress and President's palace, Morro Castle with its

epitome of three hundred years of Spanish military rule, but now quite unfortified, a typical tobacco factory, the shopping districts, the beautiful American suburbs, private clubs and the most distinctive Casino with its Monte Carlo atmosphere.

Dr. Aristides Agramonte, now the highly respected professor of bacteriology in the University of Havana, at one time was the Minister of Health in the so-called "honest cabinet" of the former President of Cuba. Dr. Agramonte entertained generously in his own home and elsewhere during the stay in Havana. At the ship on leaving he introduced relatives and friends in a diplomatic group from Colombia and Ecuador. A party was given in his honor the following night on shipboard where felicitations were extended to him by oratory and radio.

Mr. Yepes of Bogota, Colombia, legal attaché to the foreign office and member of the Colombian delegation just returning from the Pan-American Conference, was able to give those interested, first hand information about that important international meeting, especially as to the universal South American feeling against intervention by the United States.

Cristobal and Colon, Canal Zone, were reached after three days of sailing in perfect weather. After shopping tours and the unfailing hospitality of Dr. James at the Strangers' Club, the westward transit of the Isthmus was begun. Three relays were made. The first was by auto to the famous Gatun locks which in three stages lift ships to the level of Gatun Lake, eighty-five feet above sea level. The Gatun dam, including spillways, is 8,400 feet long, and backs up the Chagres River maintaining the lake level and providing the water supply for the operation of the locks. The second relay was by steamer across Gatun Lake and through the famous Culebra Cut section of the canal amidst fascinating tropical scenery and vegetable and animal life. The remainder of the trip from Pedro Miguel lock to Panama was completed by auto through delightful driveways abounding with flowers, fruits and birds. Tivoli Hotel was headquarters for the Panama stay. The City

has a population of about 60,000, the old section having the same narrow streets and quaint architecture seen in Havana. A sight-seeing trip was made, ending at the site of old Panama and the ruined tower, destroyed by the buccaneer, Henry Morgan, over three hundred years ago. Cocoanuts, cashew nuts, papaya, plantain, mangoes and many other tropical fruits were seen en route.

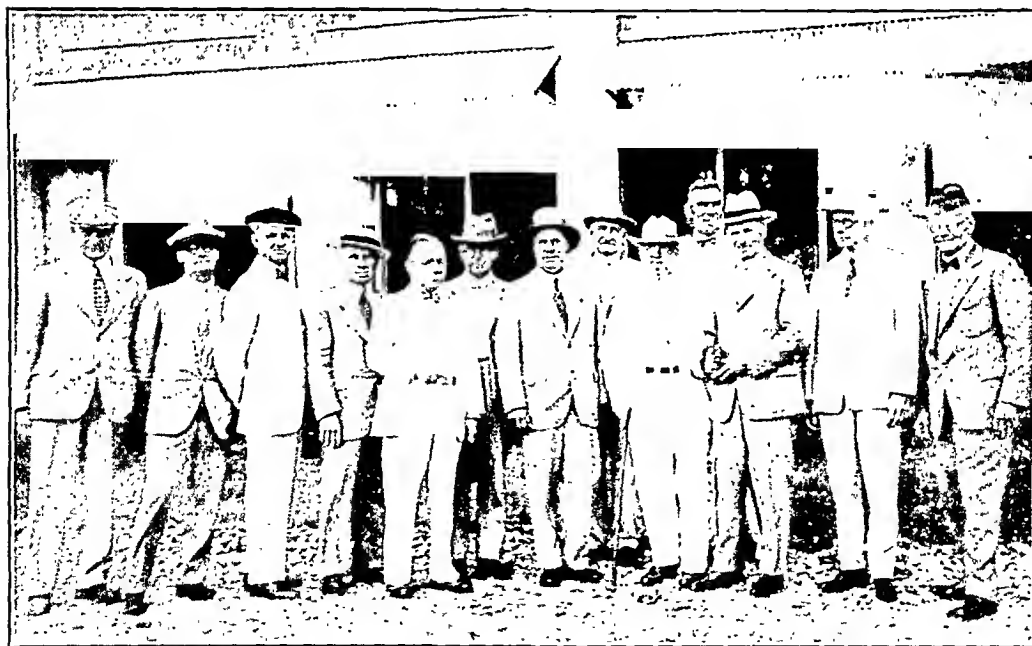
In the evening an elaborate dinner dance was given at the Union Club by members of the local medical profession, especially Dr. James, Dr. Briscoe, Dr. Reader, Dr. Avery and their associates. This was a most delightful party in an open air pavilion on the shore of the Pacific Ocean. Representative people from the city and the staff of the Ancon Hospital were present, including Dr. Paredes, an alumnus of the University of Pennsylvania, son-in-law of the President of the Republic of Panama and Minister of Health co-operating with the United States authorities in the Canal Zone.

Monday, March 19, was marked by a visit to the famous Ancon Hospital. A special demonstration of tropical diseases was given by Dr. Bates, Director of Laboratories, and others. The colon of a fatal case of amebic

dysentery was shown, illustrating the enormous thickening of the bowel in severe cases, sometimes simulating carcinoma. Various phases of malaria, including the structure of the different species of mosquitoes, a malaria-like infection of cattle, trypanosomiasis of horses, leprosy, pellagra and a collection of venomous snakes were among the things presented. The hospital is equipped with all modern facilities in X-ray, electrocardiographic and other apparatus, and is a monument to American medicine. Supt. Eklunzer and the medical staff were very cordial in their attentions to the visiting physicians. One can justly feel proud of being an American on visiting the Canal Zone and seeing the efficiency of sanitation and general administration. The return trip to Colon was made by rail. Large banana plantations and quaint native huts were seen among the mountains.

On leaving Panama, the party presented Dr. James with a Dunhill pipe and Mrs. James with a silver flower basket as an expression of appreciation of their fine spirit of hospitality.

Puerto Castilla, Spanish Honduras, was the next stop. The harbor is protected on one side by a small range of mountains



PART OF GROUP VISITING HOSPITAL AT CASTILLA, HONDURAS

5,000 feet high. An eighteen-mile railroad trip was made to the village of Truxillo, one of the oldest settlements in the new world. It gave a good idea of an inland town, the Honduranian life, the native Carib village and the surrounding country. It was very obvious that development by outside capital such as the United Fruit Company was a blessing to the whole district. The Fruit Company maintains a banana plantation there with a payroll of about 6,600 employees. There is a complete commissary establishment, a club house and an excellent hospital. At the latter, ward rounds were enjoyed through the courtesy of Dr. Phelps, Superintendent, and his associates. Malaria is their main problem. Most patients have it, either alone or complicating other conditions such as pneumonia, which often runs a long unresolved course. They believe they get good results in these cases with 20 c. c. of 1% mercurochrome intravenously. They are using 1% tartar emetic in both leishmaniasis and chancroidal infection. Ninety per cent of their cases have hook worm infestation, which is treated with oil of chenopodium and carbon tetrachloride incidental to their treatment for other conditions. Amebiasis is a less important disease at present in Castilla. Tuberculosis occurs and runs an unfavorable course. The

natives stand disease, even measles, very poorly, but recover surprisingly well from extensive injuries.

After a pleasant evening's entertainment at the club house, and witnessing the loading of 65,000 bunches of bananas on board the Cartago, the party said goodbye to Honduras.

Two days more of perfect weather and Havana was revisited for a short hour or two. Some of the party stayed over to return by way of Florida. The rest, after a few words with Dr. Agramonte who came aboard to greet the party again, and after a few hasty purchases, continued the fair weather sailing to New Orleans. During the Cruise, the party was entertained by deck games, special dinners and other social functions. The whole tour was so satisfactory that it was suggested that some similar trip be made an annual affair following the Clinical Sessions. Many close friendships will be formed within the College of Physicians, between members in widely separated parts of the country and opportunities for instruction and recreation will be provided under the most pleasant circumstances.

V. C. ROWLAND, F.A.C.P.

Cleveland, Ohio

# Presidential Address\*

(*American College of Physicians*)

By FRANK SMITHIES, M.D., Sc.D., *Chicago*

**I**N the past, the parting words of your retiring president have dealt largely with the national and international necessity for such an organization as The American College of Physicians. This vindication of our society does not require reiteration; very little if anything, can be said supplementary to the masterly addresses delivered by former Presidents James M. Anders, Harlow Brooks and Alfred Stengel. In no uncertain way, have these gentlemen defined the fields of endeavor open to The College and most potently have they emphasized for us and the curious, if not critical, the pressing urge for just such grouping of internists and research workers as now comprise our membership. Furthermore, former Presidents have practiced what they preached: no one, not intimately connected with The College adequately can appraise what of influence, time and physical energy these men unselfishly have given to advance the growth, the rating, academic and ethical, and the financial stability of our organization. Without their help your College could not have developed to its present significance: nay, it is doubtful whether it could have continued to exist. Our gratitude should be everlasting: most cer-

tainly, as time passes, the work of those pioneers will assume larger meaning when decades permit the proper perspective.

On the present occasion, it would appear not altogether useless that your speaker bring to your attention certain achievements of The College, place before you its structure and status and inform you of what is to be ventured.

In the lives of all organizations, as in the lives of individuals, it is wisdom, at intervals, to take stock, to appraise, to calculate liabilities and assets, to recognize strength but not at the expense of disregarding weakness. Only by the rigid and impartial scrutiny is advance along suitable lines intelligently to be made. In your speaker's opinion, at this session one should dwell not on justification for the existence of The American College of Physicians—such meetings as the present answer what doubt there may have been in that regard—but should survey the paths which have been trodden in order that progress along the highway before us shall continue to be travelled with dignity, respectability and usefulness.

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\*Delivered before the American College of Physicians, March, 1928, New Orleans, La.

In May of this year, the American College of Physicians will have been in existence twelve years. While in some quarters, in 1915 doubt was held regarding whether or not the College were properly launched, yet, it *was* launched. No one, honestly, can question the high motives, ideals or enthusiasm with which the sponsors of The College took up their tasks.

As a direct answer to those who criticise the early career of the College,—and it may be said the harshest criticism came from those who were least familiar with the venture—it is interesting to know that in the first five years of its existence (up to 1920) but 230 physicians and laboratory workers had been admitted to Fellowship. This group was comprised largely of physicians in New York and nearby cities. Study of the personnel at this period demonstrates that it represented practitioners of internal medicine above the average in the section embraced. The fellowship roll included a goodly number of internists of national prominence. Careful search of the roster of the early members fails to disclose a single scoundrel or irregular practitioner. I mention this, because, during its early days, the College faced such accusations and some even stronger, the echo of which injustice may be recognized even today if one have his ear close to the ground.

Beginning with 1921, at the Baltimore annual clinical week, The College became for the first time, an organization destined to include all qualified, progressive practitioners of internal medicine throughout the American continent. Such increased

scope was possible only because a wholly unselfish, disinterested group of men, who were then called Councillors, saw what advantages to internists would arise from an organization supporting the cause of the internist in the field of medicine and from the opportunity for their association in a continent-wide group. These councillors gave liberally of their experience, time and funds, so that a suitable organization for creating representative and more highly skilled internists might become possible. These councillors were fortunate in securing the advice and guidance of many of the most representative teachers and clinicians of the country. Nothing was done hastily. Indeed, it was not until 1924, nearly ten years after the College had been incorporated, that those who were interested in the movement, felt that foundations of such strength had been laid as to warrant permanency and service. There was no hurried drive for members. There was close scrutiny of applications for fellowship. Election to fellowship by the then regents represented the opinions of an eminent board regarding the desirability of a candidate. Indeed, the American College of Physicians never has carried on a "drive" for membership such as has been commonly conducted by our greatest national organizations. Many applications for fellowship came to the Secretary-General's office spontaneously or, from physicians who already had attained fellowship and were desirous that their associates do likewise. This situation exists today. Without "barn-storming" or regional or sectional campaigns, the

enrollment of the fellows has risen from 230 in 1915 to 1507 in 1928. In addition to this great fellowship roster, there are now 600 associates.

The Fellows of the College do not constitute a non-representative, incapable and unimportant group. This is demonstrated emphatically by perusal of the 1927-28 Year Book. The roster shows that approximately 40% of the total number of Fellows are engaged in a teaching capacity, either as part or full-time men. Further, by this group every first grade school of medicine in the United States and Canada is represented. In the case of numerous institutions, practically the entire clinical and research faculties, including and above the grade of instructor, are Fellows of the College. In fact, there are but four A grade institutions in the teaching of medicine in the United States and Canada whose leading clinicians are not at present enrolled on the College roster. In addition to the 40% of Fellows who are actively engaged in medical teaching, practically the entire medical and laboratory personnel of our public services (Army, Navy and Public Health), from those occupying the highest posts to those in positions corresponding to instructorship in reputable colleges, are active and enthusiastic members. The College likewise honors the only medical man in President Coolidge's cabinet. Finally, more than 90% of those Fellows who are so situated geographically as not to be in close relationship to teaching institutions are heads or important members of their staffs in first rank hospitals or clinics. In the majority

of instances, these men have a most important influence in directing and maintaining scientific and ethical standards in the institutions and communities in which they practice. Many of these men conduct important medical clinics for the instruction of brother practitioners. They are teachers in nurses' training schools, directors of municipal and state health laboratories and carry on a type of medical practice which compares favorably to that observed in any of our leading teaching institutions.

Especially has the College been wise in arranging for a group called "Associates." As at present constituted, the personnel of this group includes a goodly number of men who are connected with teaching institutions and clinics and who are enrolled as "Associates" during what might be termed a "term of probation" or "ripening". In this period, younger men can be kept in close contact with teaching, hospital, laboratory and research work, and, under the guidance of seniors of their services in their communities, approach the time when by high standards of work, ethical practice and scientific contributions, they become eligible to full fellowship in the College. This associate group is becoming and it is proper that it should become, a potent influence for encouraging, supporting and assisting the young physician desirous of making internal medicine his life's work after he has become separated from the stimulus of college, hospital and institutional environment. I look upon this "associate" group as one of the most significant agents for forwarding the best that



exists in American medicine. Previously, many internists of most excellent promise were lost to the practice of internal medicine and as contributors to our literature, because after severing the ties of university and hospital, there was not available to them an organization through which they could receive assistance and to which they could contribute by work or by attendance. It is from such men, frequently located far from so-called medical centers, that medical discoveries of the greatest worth have and may come. Our medical annals are filled with instances, where, as a result of encouragement and timely aid from more experienced seniors, new forms of disease and new types of therapy have become known. For example, a Nevada mining-camp physician demonstrates an early, if not the earliest case of pulmonary sporotrichosis; a Nebraska internist describes the new clinical entity, congenital family oedema; a northern Michigan doctor doing his best to become an internist in spite of the surgical urge of his surroundings, records the spontaneous occurrence of scarlet fever and measles and, another, far from inspiring medical contacts, contributes observations of first rank upon goitre; from a laboratory in a Michigan town of less than 30,000 comes what is now the standard precipitin test for syphilis; two Arizona physicians record and describe endemic Malta fever; a young Mississippi doctor, upon encouragement and opportunity, performs the most important piece of work upon the transmission and control of malaria since Lavarán's original thesis; our knowl-

edge of sprue and its anemia is advanced from a small North Carolina town; a Missouri physician assembles the greatest pollen collection on the continent; a previously obscure Canadian gives to the world insulin. Time alone prevents the recital of other contributions equally valuable.

The point at issue is how much progress has been lost during the past thirty years because capable men were, by environment, kept from contact with medical men of their kind and deteriorated from lack of encouragement and stimulus? Certainly, one cannot fail to grasp the importance to an "associate" of a group of fellows in his own community or state with whom he can communicate and from whom he can receive suggestions regarding the practical carrying on of work in which he is particularly interested or has an especial bent. Until the organization of The American College of Physicians in its present form, he could not receive this type of stimulus through any organization now existing on the American continent. Is it not reasonable to expect that when our roster includes a thousand "associates" who are eagerly pursuing clinical and research work in an effort to qualify for full fellowship, better practice of medicine will follow in many communities, better hospital organization will result, and from more intensive and intelligent effort, valuable contributions to our knowledge will be made?

From the foregoing, it is evident that the personnel of The American College of Physicians discounts criticism. The group represents a large section of what is best in the acad-

emic, scientific, administrative and practical field of internal medicine on the American continent. It constitutes the only great organization of internists on this continent. It is the only altruistic endeavor to recruit, stimulate and train an oncoming body of young men to keep filled the ranks of ethical, scientific medicine as their seniors choose to lighten their burdens or cease their labors.

That the ethical ideals of the organizers of the College as it at present exists well have been maintained by the Fellows after their election, is strikingly demonstrated by the fact that the Ethical Relations Committee has had to consider less than one-half dozen instances of suspected violations of the Constitution or of our oath from the date of the foundation of the society.

That the College is proving a stimulus to the young internist, is evidenced by its records: within the past year the number of applications for Fellowship and Associateship has been twice as large as in any year in the history of the organization.

One of our greatest accomplishments has been the establishment of an annual clinical week in medicine in one of the great cities of North America. In no other organization on the Continent is it possible for clinicians and laboratory workers to meet annually for a frank discussion of what is actually or is potentially of value in the field of medicine. It is true, that from time to time, national associations have attempted to hold in connection with their annual assemblies, certain clinical conferences, but also, it is true that the attempts of

none of these national organizations has been in any way successful. One has but to attend the clinics held on some of these "pre-convention days" to satisfy himself of this observation. The American College of Physicians is the only organization on the American continent which annually meets with the distinctive and definite object of profiting by a week of amphitheatre and bedside medicine or, the observation of laboratory methods in close relation to their elucidation of problems of disease.

That a clinical week in medicine was needed and that it could be made of incalculable value to the internists and teachers, is demonstrated by the increasingly great success of each annual session of the College. To be sure, there exist other organizations which meet and devote time to clinical medicine, but none of these organizations is national. Here and there throughout the land small groups of medical friends or men, who are interested in similar problems, occasionally gather as "interurban" or "clinical" clubs. These meetings are designed so that even men who every day are in contact with a large hospital material as clinicians or as teachers, find it helpful and broadening to discuss patients from the clinical standpoint, to see a man work in his own environment and to observe the social, administrative and scientific problems connected with different institutions. Valuable as these interurban clubs are, unfortunately they are limited in their attendance, largely to the very men who least need clinical or scientific prodding or guidance. Most of the attendants at these sessions already are consid-

ered by others or by themselves to be specialists in their various fields: hence, often the meetings ignore the clinical aspects of medicine and degenerate into wordy debates on abstract topics. However, the existence of these small, local groups or clubs indicates the desirability for clinical and scientific men periodically coming together for readjustment of viewpoints and ideas. If such local (gatherings are of benefit to a few, then no one can gainsay that an annual national or even international conference of internists for similar purposes is not a forward step educationally. If the American College of Physicians had done nothing else but institute and maintain its annual week in clinical medicine, it would have justified its existence.

Certainly, during the past ten years, any internist who has attended the clinical sessions of the College as held at various medical centers throughout America refuses to be satisfied with what previously he has been able to glean from the occasional meetings of local, interurban clubs and their necessarily limited scope. Is it not an unusual opportunity when an internist once a year may secure new outlooks and readjustments of his ideas by mingling with hundreds of representative medical men from all parts of America, from observing institutions and their equipment and from having demonstrated to him types of patients with which he may have been familiar only vaguely through rare contact or but from the literature? Moreover, as the program of this meeting has amply proved, is it not of inconceivable practical worth to internists and to research

workers to have presented to them disease symposia, the speakers at which are authorities in their special fields? Upon the programs of none of our national organizations with limited membership or in sections devoted to medicine in our numerically greatest associations is it possible to have assigned five half days and four evenings to an exhaustive discussion of live medical or research problems. From their very nature, other national medical societies, whether they be of research type or be great gatherings of general practitioners, cannot devote time for the thorough discussion of the various phases of internal medicine as is possible at the sessions of this College. For the clinician or laboratory worker who has a sound contribution to make, the clinical week of the College affords an unrivalled opportunity. The constant apprehension of your Regents is that ultimately attendance at these sessions will be so large that only a few cities will be capable of staging the meetings along the comprehensive lines defined by the Fellows and Regents.

Early in the organization of the College, it became apparent to your officers and regents that there was a place in the field of internal medicine for a publication devoted to the linking of clinical observation with laboratory observation and research. To the answer that the medical journalism already had covered all topics, I may say that, with possibly one exception, there exists in this country no periodical exclusively devoted to furthering the interests of internists and affiliated laboratory workers. In medical journals, the art of medicine

as exemplified by Osler, rapidly has been thrust into the background by the weird admixture of various non-related topics in their pages or by the publication of half complete, often purposeless, clinical or research investigations. Granted that all of these magazines are of value, yet, there is no question, that there is demand for a periodical which is concerned solely with the problems of the internist.

The establishment of a new medical journal is not an easy task, particularly when such journal is conducted upon ethical lines with respect to its advertising pages. Great journals are the end products of painful evolutionary effort: they cannot be built and enlarged like sectional book cases. They require healthy original concepts, skillful guidance, maturity by time, and opportunity to create affection and longing in the hearts of those they greet. Your regents have fully been alive to the situation. In their wisdom they prevailed upon Professor Warthin to assume the editorship of your official periodical, the *Annals of Internal Medicine*. Busily occupied with teaching and investigation as is Professor Warthin, yet, he entered upon his task with enthusiasm. To it he has brought unusual scholastic, scientific and executive ability. Month by month, the College has had presented to it one of the most attractive, medically and culturally valuable, and linguistically correct journals in the world. Young as the publication, is, one has only to pursue current medical literature to observe how frequently reference appears to articles originally published in the *Annals*. The excellence of Professor War-

thin's editorials is marked: not rarely they are quoted *in toto* by leading national periodicals. Book reviews and abstracts are of an unusual kind and completeness.

The circulation of the *Annals* steadily has increased. At present, even with but approximately 1500 Fellows in the College, the monthly distribution of the periodical is more than 2000 copies. With constant accessions to our membership roll and with the continued high quality and the future enlargement of the *Annals*, it is safe to say that within as short a period as two years, the journal even without advertising revenue, will not only have one of the largest monthly circulations on this continent, but will be self-supporting. Your speaker regards it as an achievement of the first order that the College has succeeded in so quietly and successfully launching this new publication. Further, the College owns the *Annals* outright and it will be the policy of the Regents to carefully guard our proprietorship.

Inasmuch as this great body of Fellows meets but annually, a few words with respect to the administrative and financial side of your organization are in order. For about two years, the College has had a thoroughly equipped and up to date central office at Philadelphia. It has been established in close proximity to the University of Pennsylvania and thus absorbs a certain degree of academic tradition and vision. At this office, equipment both with respect to personnel and mechanical appliance, is beyond criticism. Such office manages efficiently the multitudinous details concerned with applications, investi-

gations of the qualifications, academic, professional, ethical and social, of candidates for fellowship, the meetings of various executive officers and committees, correspondence relating to our publications, state and national activities, etc. With an adequate force of assistants, generously provided by the Board of Regents, the Executive-Secretary, in co-operation with the Secretary-General, conducts the affairs of our organization in an intelligent, dignified and prompt fashion. In addition to the routine details, the office arranges the annual sessions and economically transacts the financial business of the organization. It is doubtful if any organization of internists in this country has the affairs of its members so well tabulated and conducted as does the American College of Physicians. The scope of this central office is increasing. Inquiries come to it regarding post-graduate study, the meetings of scientific groups, the standardization and interpretation of laboratory tests, abstracts of literature, problems arising in hospital administration, data concerning the experience and standing of practitioners, hospital equipment, co-operative activities along various professional, social, philanthropic and ethical lines, etc. Thus, it becomes quite evident that as the College develops, its central office will require expansion if it is adequately to assume the increasingly vigorous activities of internists throughout the continent.

It will not be long before the College will require not only an increase in its office staff but even a building for the reception of its members, the

housing of its records, the maintenance of a library or a museum. Those who are intimately connected with the affairs of the organization forecast that these requirements can not long be postponed. The College will not go backward; it cannot stand still; it must go forward. In going forward, its activities will broaden far beyond our present conceptions. In view of these circumstances, the question of a permanent home for the American College of Physicians requires immediate consideration. Definite plans toward such should be made. While it may be years before the home of the American College of Physicians will rival that of its sister organization across the water, or of local institutions, as the College of Physicians of Philadelphia, yet, the increase of its affairs will compel expansion. It behooves the Fellows and the executive officers to plan broadly so that at the time of accomplishment, the College will be in possession of quarters commensurate with the dignity, responsibilities and achievements expected of the organization.

The office of the Executive Secretary, together with the assigned Committees and the Regents, have achieved a noteworthy success during the past year in the issuance of a Year Book and a Bulletin of the College. Especially needed was a Year Book listing the Fellows and giving information about them. I know that, in many quarters, perusal of this Year Book has occasioned surprised comment: the surprise being due partly to the excellence of the arrangement of the Year Book but more especially

to the revelations which the Year Book contains regarding personnel.

During the past five years, the College has worked in such a quiet way that many of those who, from ignorance, prejudice or habit have criticised the College were not aware until the Year Book appeared, of the great strides in membership which have been made. The Year Book potently has demonstrated to the internists of North America the wide geographic range of College membership, the high character of its personnel and, incidentally, the interest which internists have taken in an organization devoted exclusively to forwarding their own betterment. This Year Book has become a volume largely in demand in colleges and libraries, newspaper offices and among the medical profession. The volume has proved of great practical worth to physicians in a country where travel over long distance is so common. Patients no longer need be told merely to "see a doctor" in a far distant city but through the Year Book they can be given a definite list of competent internists in the leading cities of our various states and provinces; their physicians can now be assured that his patients will receive skilled care and gentlemanly attention. If physicians heretofore have felt it worth money to subscribe to Year Books, listings of "experts," etc., issued by commercial organizations, surely it is a great accomplishment for the College to have made available to them a Year Book published on a non-commercial basis, a book not merely listing men as "experts" but what is more valuable, namely, data from

which it is possible to appraise the professional and social qualifications of far distant practitioners.

The financial status of the College has been but rarely brought before you. It would seem desirable that you have knowledge what your College has accomplished in this regard. Perhaps, you will be interested to know that up to six years ago, the financial status of the College was extremely precarious. There had been no attempt made to acquire funds even for current expenses and certainly none to accumulate a surplus. Much of the expense concerned with the annual meetings, the administrative offices, travel and the like were borne by interested officers or councilors. It was seen, however, that no organization could exist long on such a footing. Through a wise policy instituted about five years ago, and most ably carried out by your Treasurer, the College steadily has accumulated, without donations, contributions or a noisy campaign for funds, a most creditable surplus. Its present assets exceed \$65,000. It is able to finance its enterprises and to pay its bills promptly enough to get discounts. Certain of these funds are segregated as an Endowment Fund. The affairs of the College are conducted on a strictly budget basis and every effort is made to carry on most economically. Thus, the money contributed by Fellows is not wasted. Every candidate upon payment of his initiation fee, can feel assured that what he has paid is not lost but is held in trust for his benefit and to foster all that is best in the advancement of internal medicine.

The Constitution and By-Laws specifically provide for the creating of the endowment fund. The purposes of such funds would seem to be not only provision for a permanent home for the College and for maintenance but to make available a sum which the College can employ for encouraging research and for education. It is only within the past year that the Regents have had opportunity seriously to consider putting forth efforts to create an endowment fund of substantial proportions. Already you are familiar with the opportunity which has been given to the Fellows of the College to subscribe, either in lump sum or by installments for life memberships. The sums derived from these life memberships can, almost in their entirety, be placed in the endowment fund. If but one thousand of our Fellows systematically set about the purchasing of life memberships, within three years the Endowment Fund will be sufficiently large as to enable the Board of Regents to provide handsomely toward the carrying out of the purposes for which this fund is intended.

Apart from the academic and clinical attributes of the personnel of the College, it seems highly important that every Fellow appreciate the significance toward extending the influence of the College which a strong financial rating will insure. Much of the success which has attended the efforts of our sister organizations can be attributed to these organizations having available the means whereby they could effectually attack the problems requiring attention and solution. There should be no urging of Fellows

to contribute to the Endowment Fund: its creation should not entail great hardships upon anyone. However, it is well known that many of the Fellows are amply able from savings of current earnings to purchase life memberships. These men should feel that it is a privilege thus to contribute something toward the permanency and the expansion of the organization to which for years a small group of Fellow members have given liberally of time, physical effort and money. To a letter recently sent to each Fellow, there has been a noticeable stimulation of interest in the Endowment Fund and a creditable number of Fellows have either paid for life memberships in full or have arranged to take care of payments at intervals. To these men the organization owes deep gratitude. It is expected that in the coming months an increasingly great number of Fellows will do their bit. It is realized that there is a group in the College who on account of the nature of their occupations as teachers, health officers and the like will not be in position to make substantial contributions to the Endowment Fund. A suggestion is made that in these circumstances, men so placed keep the Endowment Fund of the College in mind on occasions when public spirited laymen of their acquaintance express desire to do something in a substantial and material way for the advancement of medical practice and science. In all probability, in every community there are men willing, and ably so, to assist, provided they know along what lines assistance may properly be given. It is the duty of Fellows to ac-

quaint substantial laymen with the opportunities for giving offered by the College and it might be well within the bounds of propriety, when plans have matured, to solicit subscriptions from laymen toward the purchase of a suitable college building. It would be only gratitude on the part of the College that the names of such contributors be perpetuated in enduring fashion by appropriate tablets on the walls of our permanent home.

Time does not permit more than a brief resumé of what the special committees of the College have accomplished during the past two years. I have already acknowledged the debt which the College owes to the Committee on Publications and Year Book for the thorough fashion in which they have worked in order to present to us *Annals of Internal Medicine* and the *College Year Book*. These men have been greatly helped in their tasks by the support of a loyal and enthusiastic Board of Governors, in fact, in some states, the governors have themselves been largely responsible for the accuracy of data, favorable sentiment toward the College and a steady flow of fellowship applications toward the Executive Secretary's office.

A committee which has been most active and helpful is that concerned with hospital efficiency. Under the guidance of the Board of Regents, this committee has considered exhaustively how the College could be of help to its Fellows in exercising some form of control over the medical, as distinct from surgical, routine and practice in our hospitals. It has been

thought wise not to rush hastily into any such program, nor to present to you, to other interested organizations and to hospitals, a program which would be incomplete, a reduplication of effort or an annoyance to the institutions. As you well know, the so-called standardization plan of the American College of Surgeons—the "minimum requirements" program—has meant much toward increasing morale, efficiency and equipment in many of our hospitals, particularly hospitals not located in the larger cities. The data accumulated by the American College of Surgeons has been collected at great expense and effort. The co-operation of hospital authorities has also entailed work and sacrifice on their part. The American Hospital Association likewise has collected much data and has been an influence for good throughout the country. The American Medical Association has made a complete survey of the country's hospitals from the standpoint especially of their furnishing suitable institutions for the training of internes, nurses and with regard to their fitness as places for graduate instruction. One can readily see, therefore, that any activity of the American College of Physicians must be cautiously and intelligently directed. If it is not, then institutions will be annoyed by what they regard as a re-canvass of the field already well covered and in such circumstances many hospitals will be antagonistic. The organizations already mentioned have done most creditable work and the American College of Physicians, by co-operating with them in what already has been done, doubtless can



prove of service. However, no organization has, as yet, surveyed our hospitals with regard to the proper handling of non-surgical patients from the standpoint of how the internists consider these patients should be handled. In fact, the programs for management and efficiency which have been proposed to our hospitals have been instituted as blanket schemes for management and such schemes have emanated largely from a surgical group or from a lay or office working group not intimately aware of the needs of the internist. Thus it follows, commonly, that in the working out of plans proposed, most hospitals are surgically "top heavy." To be sure, the internist is a member of the staff and is held responsible for the type of work which he carries on, but he is not given a position to carry on his work along lines which he may think desirable. Rather, he is compelled to fit himself into a scheme which frequently enough does not suit his requirements or which is not what he considers the best that might be devised.

From communications which have frequently come to me, I gather that the internist is not satisfied with the position of subordination to which he is subjected in the vast majority of our hospitals by the workings of so-called standardization plans as they now exist. Frequently enough, he is not consulted with respect to staff members, equipment, laboratory personnel, laboratory procedures, autopsies, staff meetings or records. It is not to be wondered that such internist is not an enthusiastic staff member, does not support the monthly clinical confer-

ences and takes relatively little interest in inter-departmental activities. Your committee has endeavored to find some way in which the College could help. Co-operation with already existing organizations concerned with hospital management and practice has been offered, but in no instances has this co-operation been proffered along lines which would make the endeavor, so far as the College were concerned, co-operative along lines of equality.

At present, it is the sentiment of your committee that the College should in no way hamper the hospital activities of sister organizations but should not accept in these activities a subordinate position. Your committee feels, that without great expense in each state or province, the hospital situation with respect to the internist can be canvassed through the supervision of one of your Fellows, most appropriately the Governor of the College for the State and by this means within a reasonable period of time, the College could be aware of what actually is needed. Each Fellow would have to play his part in this activity and if supplied with suitable direction and comprehensive forms upon which to record observations, in due time information of great value could be collected. From these original sources, your committee and the Regents would be in position to propose a simple and definite plan whereby the defects existing in our hospitals today satisfactorily could be remedied.

The question of College activities for the Fellows generally, between annual sessions, repeatedly has been brought to the attention of your Regents and officers. There has been a

desire expressed by many that the College institute and supervise short-session, sectional, clinical conferences to be attended by Fellows located in groups of conveniently adjacent states or provinces. It has been felt that these gatherings would do much to stimulate clinical and scientific medicine and, from such sessions, the hospital needs of the various communities accurately could be appraised. Further, these sectional meetings would indicate to the hospitals and the communities in which they are situated, that in the field of medicine, generally, there actually does exist a group other than the surgical. It is only by making hospitals and communities, what I might call "internist conscious," that our influence and our organization will become potent and direct.

I feel that during the coming year, definite steps should be directed toward arranging a program for at least mid-session gatherings of internists and these gatherings should be sponsored by the College. It should be known in the various communities that they *are* sponsored by the College and in all instances the sessions should be attended by such officers, regents and governors as are available. The institution of sectional meetings and the direct canvass in each locality of the medical facilities of hospitals will prove too great a task for the home office adequately to bear. Consequently, it is the opinion of your retiring President that in the very near future, the College should have available to further the local and national interest of its Fellows, a full-time, paid, medical man, not a practitioner, but thoroughly ex-

perienced, who would serve as a field secretary. Only in this way is it, in my opinion, possible for the College to extend its influence in communities, to know the needs of medical men in a medical way, to accumulate data for your officers, regents and general headquarters, which will be reliable and complete. The time has come when the usefulness of a medical, field-secretary can be demonstrated to every Fellow of the College in a manner which is practical, and along lines for which there is need. I earnestly hope that those who have been entrusted with the responsibility for furthering the interest of the *average Fellow* in the *average* community of this country and Canada, will see to it that, without delay, there is supplied the field-secretary for whom I can see so great a need.

Finally, it is a pleasure for me to express to you the privilege which you have given me for so long a time to work among you and to thank the Fellows, officers and regents for the co-operation which they have given me in my efforts to build the College along lines which will be substantial and permanent. It has been a great satisfaction intimately to come into relationship with so great a number of internists and laboratory workers on the American continent. This personal contact has been extremely broadening. It has been a potent influence toward counteracting whatever pessimism I may have had with regard to the practice of internal medicine. I have found, in all sections of the continent, that internists were ethically and morally sound; they were good cit-

izens, they were gentlemen; some of them were prosperous. But the greatest inspiration has come from the observation of how universally well the internist was practising his art. One who has confined himself only to office and laboratory practice in the great medical centers, can have no appreciation of what is being accomplished by internists in communities of smaller size and influence, unless, as fortunately has been my lot, he is able to see for himself how, in other communities, the daily work in office and hospital is carried on. Frequently, in the most unexpected places, I have had opportunity of observing a type of work of the most superior kind, in fact, work of such excellence that, if it were done in connection with one of our larger institutions, would bring to the physician a reward both scientific and practical. I

feel that the American College of Physicians has been an influence in stimulating throughout the land among many internists the daily performance of duty along highly commendable lines. It is my opinion that the influence of the College in this regard has only begun. But it *has* begun and I regard it a great achievement to have made available to internists an organization for their own expression, for their betterment, and to stimulate them to greater accomplishment. But, lastly and best of all, in the banding together of internists throughout the Americas, there has followed, through the College, the development of a spirit of individual and group loyalty, of scientific, honest and sportsmanlike conduct which bespeaks great advances, social, professional and scientific, in the not distant future.

# Adaptation and Compensation as Origin of Disorders\*

BY JULIUS BAUER, M.D., *Professor of Internal Medicine at the University of Vienna, Austria*

**M**R. President, Ladies and Gentlemen, I appreciate highly the great honor of having been invited by the Board of Regents of the "American College of Physicians" to read a paper at this annual meeting and I am deeply indebted for having this opportunity. To a research worker and medical teacher it is the greatest satisfaction to see his work recognized and to get in personal contact with many representatives of the profession, in order to communicate them some of this work. But there is a slight difficulty. One's own research work must necessarily deal with a more or less limited, narrow field of medicine and I could not possibly hold the interest of all the members of the College if I spoke on a special problem of the many ones which have fascinated me for many years.

Therefore I thought to review with you a greater number of pathological conditions in order to throw some light upon them from the general biological and special points of view. Sometimes it is more interesting to reveal a new side of an old and well known thing than to get acquainted with new things.

We are fascinated every day at the patient's bedside and in the dissecting-

room by the marvelous functional and anatomical changes of an organism induced by a primary lesion or disturbance of an organ showing the character of adaptation or compensation. This term includes the conception of usefulness of these changes and bears upon each process which tends towards healing of the primary lesion. But this teleological conception in accordance with and innate to the human mind prevents us frequently from detecting a more complicated mechanism and from becoming aware of the fact that we have to pay for the originally useful adaptative process. We have to pay either on account of some accidental or obligatory by-effects of this process or on account of its exaggerated intensity. The original usefulness of the adaptation recedes entirely in the background and the adaptative or compensatory character of the present pathological condition is scarcely to be revealed. Quite a great number of disorders are to be attributed either to some undesirable and fateful by-effects or to an exuberance of adaptative processes.

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\*Lecture delivered before the American College of Physicians, March 5, 1928, New Orleans, La.

Arterial hypertension in a case of nephritis may certainly be useful and facilitate the excretion of urine. The higher the pressure in the renal arteries the better the filtration process in the glomeruli. We do not yet know the actual mechanism of the genesis of such a renal hypertension but we may call it adaptative because of its apparent usefulness. But this adaptative process involves the obvious unpleasantness and the danger of an arterial hypertension. The patient may be saved from a renal insufficiency but he may suffer from headache, dizziness, aortalgia and all the other well-known consequences of arterial hypertension and may even die from apoplexy or cardiac insufficiency. The development of vicarious emphysema of one lung in a case of destruction of the other lung is without any doubt a compensatory process because it enlarges the respiratory surface through the distension of the alveoli. But such a permanent distension of the alveoli is easily followed by a destruction of the septa with a subsequent diminution of the capillaries. This renders the pulmonary circulation more difficult and requires a greater effort of the right ventricle. An originally useful compensation has become a danger for the heart and may shorten the life of the patient through an insufficiency of the hypertrophied myocardium. It is a matter of scientific discussion why an hypertrophied heart muscle does not possess quite the same power of accommodation to an increased effort as a normal heart muscle. A discordance between the increased mass of the myocardium and the scarcely or not at all increased mass of the specific

conductor system has been given as the reason for the latter. One took into consideration the proliferation of the fibrous tissue in the myocardium induced by the increased pressure upon the inner wall of the heart. At any rate it is obvious that an adaptative process as heart-hypertrophy in cases of valvular lesions or arterial hypertension involves at the same time a lowered functional accommodation and may herewith give rise to an insufficient heart function.

We owe to the Viennese clinician Wenckebach (1) the remarkable

(1) K. F. WENCKEBACH, *Med. Klinik*, 1928. Nr. 1. p. 1.

viewpoints concerning the interrelationship of advantageous and disadvantageous consequences of a cardiac insufficiency. He pointed out particularly how useful a congestion of the liver may be to the patient whose right ventricle became insufficient. As the liver is able to hold up to 1½ liters of blood like a sponge it relieves the cava inferior and subsequently the right heart of a considerable amount of blood, and prevents a stasis in the more peripheral part of the cava with a subsequent inundation of the tissues by edema. But such a patient with an adaptative liver congestion and therefore still sufficient heart action may complain of a pressure feeling in the right abdominal side or may become dyspeptic on account of a stasis in his portal circulation, particularly in his stomach. In cases of insufficient action of the left ventricle a stasis in the pulmonary circulation may even prove fatal by the danger of a lung edema, but only as long as the right ventricle

works sufficiently and its output is not diminished, the patient is less dyspneic, the right ventricle fails to discharge its whole contents the congestion in the lungs is diminished, the patient is less dyspneic, he is not in the danger of suffocation any more but he has to pay for it with congestion of the liver and its consequences. Sometimes it happens that digitalis-treatment improving only the right ventricle in such a case is followed by a diminution of the liver congestion but at the same time there appears an increased dyspnea. In addition to that it is worth mentioning what Wenckebach (2) pointed out

(2) K. F. WENCKEBACH, Wien. klin. Wochenschr. 1928. Nr. 1. p. 1.

concerning the relief of the dreadful pain of an angina pectoris by a beginning insufficiency of the left ventricle. He gathered rather remarkable arguments in favor of the supposition that this pain is due to a distension of the aortic wall and coronary arteries through a constriction of peripheral arteries. This distension decreases as soon as the energy of the left ventricle is diminished. Whether this theory is accepted or not, we must perforce acknowledge the interesting old experience that a beginning insufficiency of the heart muscle stops a stenocardiac attack; that is to say it is an adaptive process referring to the attack, but this adaptation may be rather dangerous to the patient and cost him even his life. In cases of chronic heart insufficiency following attacks of angina pectoris digitalis treatment may improve the heart but will at times release those attacks anew (Wenckebach 2).

When a case of renal insufficiency with a lowered power of water and salt elimination develops a general dropsy then this dropsy is to a certain extent an adaptive process for the kidney, but it may become fatal for the organism on account of different possibilities which arise from such a condition. It is a well known fact that an increased number of erythrocytes is not infrequently to be met with in cases of chronic cardiac insufficiency. The mechanism of such an erythrocytosis is still a matter of discussion, but doubtless we may consider it as an adaptive process in order to compensate for the deficient transport of oxygen-carriers by their increased amount. The same is true of the erythrocytosis in cases of chronic bronchitis with emphysema, where it compensates for the deficient reception of oxygen just as in high altitudes or under a low atmospheric pressure. But in cardiac cases as well as in cases of emphysema such a compensatory erythrocytosis is at the same time disadvantageous on account of the increased viscosity which makes the heart work more difficult.

We owe to the physiologists A. Fick and O. Frank the knowledge of the fact that the contractions of a muscle and especially of the heart muscle are up to a certain limit the more intensive and energetic the higher the initial tension, that is the filling of the heart, and the greater the load, that is the arterial pressure. This touches upon the riddle of the heart's accommodation and its reserve power. Therefore it is an adaptive process if a collapsed man's heart shows di-

minished contractions. Since the whole blood is filling the dilated blood vessels of the abdominal cavity; the physiological stimuli of the heart muscle, its tension by the contents and the peripheral blood pressure are markedly diminished. But this adaptative mechanism may cost the man's life, if the heart does not contract sufficiently to maintain the circulation. It is to a certain extent a sort of chronic collapse as Wenckebach (2) described in some cases of enteroptosis. The flabby abdominal wall, the insufficient action of the diaphragm and subsequently of "the abdominal press" brings about a permanent overfilling of the splanchnic blood vessels. Tachycardia, palpitation, general weakness and tendency to fainting are the consequences of such a condition and are at least partially due to an adaptative heart alteration.

Anemia is compensated by more frequent contractions of the heart, but the tachycardia may be a source of subjective disorders and is not without importance for the heart condition. We credit Yandell Henderson, Haggard (3) and their associates for hav-

- (3) Y. HENDERSON AND H. W. HAGGARD,  
Journ. of the Amer. Med. Assoc.  
1922. vol. 78, p. 697.

ing elucidated another compensatory process in cases of acute posthemorrhagic anemia. An increased air hunger and hyperpnea are well known compensatory symptoms after a hemorrhage and even a small loss of blood from the circulation induces a marked increase in the pulmonary ventilation. This sort of augmentation of the oxygen-intake is certainly useful as the

number of oxygen-carriers is diminished. But Henderson taught us that this adaptative process involves at the same time a danger. First the vigorous breathing as a considerable muscular exertion requires additional oxygen which is wanting, and secondly it causes what he called acapnia. Excessive breathing ventilates off an abnormally large amount of carbon dioxide and leaves the blood abnormally alkaline. In compensation, alkali then begins to disappear from the blood and is carried away partially by the kidney, but most of it passes into the tissues to be stored there in a way not yet fully understood. It has been pointed out by Henderson (3) that it is chiefly this disturbance of the acid-alkali balance termed acapnia that may become fatal in exsanguination. In any case we have independently of theoretical explanations to acknowledge the statement that an originally useful, adaptative process as the hyperpnea after a hemorrhage brings about a disadvantageous by-effect.

Inflammation is generally spoken of as an adaptative process concentrating the defensive power of the organism upon a point exposed to the danger. But its consequences are usually the starting point of disorders. That holds true for the actual fight in the form of an acute or chronic inflammatory process as for the devastated and insufficiently restored battle-field in the form of a scar. It needs no further detailed explanation how far fever with its consequences for the organism, how far the production of inflammatory tissue of unspecific or specific character as a tubercle or gumma and

the development of shrinking, dragging or constricting scars represents the typical combination of an adaptive primarily useful process with disadvantageous by-effects of this very process. In certain organs a destruction and loss of parenchyma may be compensated by a powerful regeneration as it is to be observed in the liver. But even such a compensatory regeneration may be the origin of new disturbances. We learned through the investigations of the late Viennese pathologist Kretz that the regenerating liver tissue shows quite an irregular and disordered structure without normal relationship of blood-vessels and small biliary vessels. This discordance in the regeneration is the cause of a new nutritive damage of the regenerated parenchyma and initiates its degeneration as soon as it has been built up. A few years ago G. B. Gruber drew our attention to this automatic mechanism of regeneration and degeneration of the liver in cases of liver cirrhosis. From our point of view it is an interesting illustration of the insufficiency and incompleteness of an apparently compensatory process involving at the same time the source of new destruction and new disorder.

So far we have given some illustrations of unwished-for and fateful by-effects of adaptive and compensatory changes in the organism. In the following we shall try to demonstrate injuries and disorders due to exuberance of adaptive and compensatory processes. In spite of their frequency we should wonder at the usual precision of adaptive reactions determined exactly in their intensity by the releasing stimuli. The most common and strik-

ing instance is the anaphylactic hypersensitiveness. It plays an important role in the human pathology not only in the usually so-called allergic hypersensitive condition as asthma, urticaria, angioneurotic edema, eczema, gastrointestinal disturbances and perhaps migraine, but also in infectious diseases or in certain cases of rheumatism. Anaphylactic hypersensitiveness originates from the inherent ability of the organism to produce antibodies as a defence against heterogenous protein and probably also some other substances that are foreign and therefore not harmless for the body. Hypersensitiveness is the result of this certainly adaptive property, but it may dominate in many clinical pictures and illustrates sufficiently how an originally adaptive process creates different sorts of disorders by its useless exaggeration.

The mobilization of leukocytes in certain infectious conditions is an adaptive reaction of the organism making it easier to fight against the bacterial intruders. In exceptional cases this mobilization is exaggerated, the adaptive stimulation of the leukopoëtic system releases a hyperactivity of this system surpassing by far the demand of the organism and producing a pathological condition which we know as acute leukemia. This mechanism of a social and anarchistic independence of certain organs and functions released by an adequate, adaptive stimulation is not quite infrequently the origin of serious disorders particularly in endocrine pathology.

A hyperactivity of the thyroid gland for instance is considered as a useful



adaptative reaction in many infectious processes. Typhoid or acute rheumatic fever, dysentery and other bacterial conditions seem to be combatted more easily with the help of the thyroid gland. French authors go even so far as to recommend a thyroid treatment in refractory cases of acute rheumatic fever not showing any benefit from salicylate treatment or an increased volume of the thyroid gland. Experimental medicine supports this view to a certain extent as we have learned that all cellular activity including the production of antibodies is stimulated by the thyroid hormone. But how frequent are the cases of hyperthyroidism of all degrees up to the classical exophthalmic goiter appearing after such a fight against a bacterial infection! Certainly we find as a rule in those cases of exuberant adaptative reaction of the thyroid upon infections an explanation for this exuberance. Those individuals were disposed to an exaggerated thyroid hyperactivity and betrayed this individual disposition before the releasing infection by scarcely indicated rudimentary signs of hyperthyroidism, they always had been nervous and irritable, had a tendency to tachycardia and sparkling eyes, perhaps also a slight swelling of the thyroid, and their family history reveals some other members affected by thyroid hyperactivity. It may be also learned by personal observations that a great psychical shock just previous to the onset of the infectious disease was an additional etiological factor of the hyperthyroid condition, but the chief point is at all events the exuberance of an originally adaptative reaction. The

thyroid does not obey any more its physiological regulatory mechanisms, it does not care for the thyroxin-requirement of the organism. If we look for focal infections in cases of hyperthyroidism in order to remove them we try to get rid of the primary releasing stimulus, but we do not succeed always as soon as the anarchistic independence of the thyroid has surpassed a certain limit.

The fearful but grandiose starvation experiment of the war showed that the thyroid as well as the gonads undergo a marked atrophy, manifest not only to the pathologist, but also to the clinician. But it is of the greatest interest from the aspect of adaptative mechanisms that this diminution of the thyroid activity in starvation is a useful condition saving energy and perhaps the life of the undernourished organism. One would not have expected that human beings can be maintained alive with such a minimum of food but one found that the basal metabolism of those starving individuals was markedly diminished without any doubt on account of the adaptative hypothyroidism. It is the very opposite of what we observe in overfed individuals and what is called luxury consumption and due to a hyperactivity of the thyroid gland, because of its disappearance after thyroidectomy (E. Graef). Everywhere in Central and Eastern Europe cases of hypothyroidism and myxedema were to be seen more frequently during the particularly bad time of food supply. But these cases were not the most starving and most endangered, they were apparently disposed to a hypofunction of the thy-

roid even before the undernourishment and fell ill as soon as the moderate insufficiency of food supply released an exaggerated adaptative inhibition of thyroid function. We have to add that the thyroid and gonadal atrophy in starving individuals is not purely a corresponding part of a general atrophy of the whole body, as we know that under the same conditions the suprarenal cortical tissue undergoes a marked hypertrophy (McCarison). An analogous proliferation has been found recently in the Langerhans' islets of the pancreas (Jorns 4) and it agrees entirely with this

- (4) G. JORNS, *Deutsche med. Wochenschr.* 1927. Nr. 32. p. 1339.

statement that the blood sugar of a starving person shows a marked diminution (M. Freund 5). Every ex-

- (5) M. FREUND, *Zeitschr. f. physikal. Ther.* 33, p. 133. 1927.

perienced physician knows the type of extremely stout people with symptoms of hyperthyroidism. It is unpleasant to meet with this clinical syndrome on account of the impossibility to apply a thyroid treatment in order to reduce the body weight. But we agree entirely with H. Zondek (6)

- (6) H. ZONDEK, *Klin. Wochenschr.* 1927. Nr. 17.

who considers the hyperthyroidism as a compensatory process fighting against the obesity. We have only to add that such an exaggerated adaptative reaction may be more dangerous for the patient, than the primary releasing obesity.

If we see acromegaly appearing during and after a pregnancy or in

addition to myxedema then we may also think of an exuberant compensation. Pregnancy as well as an insufficient thyroid function are adequate stimuli for the anterior lobe of the pituitary gland. I pointed out in 1917 (7) that a slight or moderate hyper-

- (7) J. BAUER, *Konstitut. Disposition zu inneren Krankheiten.* Berlin, Julius Springer, 1917. 3d edition 1924.

thyroidism as well as a diminution of the gonadal activity seem to be useful adaptations of the organism in its fight against a tuberculosis. It would go too far to discuss here in detail the observations and arguments allowing this statement. But today it interests us that exceptional cases with a cured or at least successfully combatted tuberculosis had to pay for this good result with the consequences of an exaggerated adaptation and developed hyperthyroidism or had lost their gonadal activity.

Exaggerated compensation is finally to be taken into consideration also in cases of benign or malignant neoplasms. From the exuberating callus and the keloid we see transitions leading to some types of neoplastic conditions developed on the basis of an exuberant reparative process.

I think it needs no further enumeration of analogous pathological processes and disorders which may be attributed quite generally to a primary compensation and adaptation of an entirely different and even rather distant pathological event. What we have discussed seems to be quite sufficient in order to recognize the far-reaching significance of always the same principle and mechanism in the

production of functional or morphological disturbances. A thorough analysis of pathological conditions reveals not infrequently such a chain of primarily adaptative and compensatory reactions inducing various disorders either by their accidental by-effects or by their not sufficiently checked and regulated intensity.

In the beginning of this paper I mentioned that the term adaptation and compensation involves the teleological conception of something useful.

The true naturalist is always shocked at a teleological contemplation of natural processes. He likes to understand only the mechanism and its causation but holds his hands off from a supposed aim and purpose of this mechanism. But even a naturalist is always a human being and can not overwhelm his own human nature and mind, he is pleased with such a teleological consideration even if it surpasses the limits of his science. All the grandiose processes observed in clinical pathology and studied by the means of chemical, physical, anatomical, biological methods they reduce to a teleological contemplation beyond the real scientific basis. It is without any doubt an immanent characteristic of the human spirit not to describe only the hypertrophy of the overstrained heart muscle or of the left kidney after the removal of the other, not to study only the mechanism of the development of a collateral circulation after the obstruction of a blood-vessel, but to recognize the usefulness of such a reactive process for the organism and herewith its apparent aim.

It was the great Viennese clinician

Nothnagel (8) who delivered an ad-

(8) H. NOTHNAGEL, Wien. med. Wochenschr. 1894. Nr. 15.-19.

dress, at the International Medical Congress in Rome in 1894 on the adaptation of the organism in pathological conditions and came to the conclusion that every apparently adaptative and compensatory process is originally aimless and is the natural consequence of the changed situation, of changed influences and stimuli. General physical, chemical and biological laws govern and regulate all these processes which as a rule appear to be, and are useful, indeed, but which are not always so in any case to be observed and which may be even disadvantageous in other cases. The varying requirement of the functional activity of an organ is able to regulate this activity and the varying activity has an influence upon the morphological structure of this organ. So we see regeneration, hypertrophy or atrophy of a parenchyma as the consequence of the organism's varying requirement of its special function. But why all these physical, chemical and biological laws provoke finally alterations of a regularly useful character, that is a question beyond the limits of the human mind. So far lead the conclusions of the pure mechanistic aspect of Nothnagels!

What we have pointed out here is an addition to this conception. Nothnagel had mentioned only some of the possible detriments caused by apparently adaptative processes. G. B. Gruber (9)

(9) G. B. GRUBER, Münchn. med. Wochenschr. 1924. Nr. 38. p. 1316.

spoke of adaptative disease in order to emphasize the disadvantageous consequences of some adaptative structural changes of a parenchyma. We intended to demonstrate that the usefulness of apparently adaptative and compensatory processes is as a rule relative only to one special function and must be paid for by the organism. The fateful by-effects or the consequences of an exuberant compensatory reaction may rule the situation. The term compensation is no more correct and should no more be used in

such a case. We see in pathology as everywhere in nature that the teleological aspect of usefulness is always the product of the human mind only and we have to be conscious of this statement. This holds true particularly for our therapeutic activity which has to support the useful spontaneous reactions of the organism and has to suppress their dangerous by-effects and to inhibit their exaggerations. Let us hope that future medicine will find out all the ways of doing so.

# Multiple Myeloma\*

By DAVIL P. BARR, M.D., *St. Louis*

**A**LTHOUGH the disease known as multiple myeloma has held a fascination for many observers, knowledge of its nature has progressed very slowly. During a period of more than seventy-five years, less than 200 authentic cases have been reported. It was recognized as early as 1848 when Henry Bence Jones saw with Sir James Watson a patient whose urine contained a strange protein which he described as the "hydrated deutoxyd of albumin." Two years later, the clinical history of this same patient was detailed by McIntyre under the designation of *mollities osium*. The association of multiple bone lesions with the unusual protein of Bence Jones was thus clearly established but 35 years passed before a second case was recorded. The paper by Kahler in 1889 offered the first adequate clinical description and marked the beginning of the accumulation of authentic cases. The condition is sometimes known as Kahler's Disease.

During the past three years, it has been our good fortune to see several cases of multiple myeloma. Time permits us today to consider only one, a case which, however, may illustrate some of the difficulties of diagnosis and of classification. Before present-

ing the case, it may not be superfluous to detail some of the more striking features of multiple myeloma. It is admirably defined by Ewing as a specific malignant tumor of the bone marrow arising, probably, from a single cell type and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastasis, albumosuria and a fatal termination. Any bone may be involved but the ribs and sternum suffer most often while vertebrae, skull, femur and humerus are less frequent sites. Although the lesion is always primary in the bone marrow, the cortex may suffer active absorption. Extension through the periosteum and the surrounding tissue is not common.

Pain is the most constant symptom. It is often excruciating and may occur wherever bones are effected. It is frequently diagnosed as neuritis, lumbago, pleurisy, sciatica or sacroiliac strain. It may even be mistaken for osteomyelitis, a diagnosis rendered not unlikely by the intermittent and occasionally high temperature which may accompany the disease. Skeletal fractures from most trivial

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\*Presented before the American College of Physicians, March 5, 1928, New Orleans, La.

causes are frequent. The nutrition of the patient may be long maintained but as the end approaches extreme emaciation is the rule. There is often a marked secondary anemia. Bence Jones protein, perhaps the most widely known feature of the disease, has been reported in only about 40 per cent of cases. While this low figure is due in large part to the inclusion of cases in which the test was not done, it is nevertheless true, that albumose may in certain cases be persistently absent. In the carefully studied series of the Mayo clinic it was found in 80 per cent of the cases.

The patient whom we shall report today was a salesman for a refrigerator company, 49 years of age, who entered Barnes Hospital on May 12, 1927, complaining of severe pain in his right lower chest and in the right hip and thigh. Four months before, in the early part of January, he had contracted a distressing cough which was followed a week later by a sharp pain in the chest. The cough persisted until the end of January when he was forced to go to bed. At this time he had a high fever, more violent pain in the chest as well as general aching. His condition was diagnosed as influenza. He was taken to a reputable hospital where he was told that a rib had been fractured. There followed a period during which he attempted to continue his work as traveling salesman. The pain in his chest was constant and distressing. He sought medical advice in Philadelphia and in New York. Finding no relief he returned to St. Louis but soon left for more trips East and South. He saw several physicians. He was treated

for "neuritis," for fractured rib." His last physician after repeated X-ray pictures told him that his chest was not affected but that he probably had cancer of the prostate. The pain in the right hip and thigh started only a week before admission and followed a fit of laughter. The pain was excruciating and kept him from moving his leg. It was the immediate cause of his admission to the Hospital. Nothing in his family history or in his antecedents seemed to be relevant to this trouble. Examination revealed the appearance of chronic illness and the effect of prolonged pain. Although the man had lost 20 pounds in four months he did not look particularly ill-nourished. On the sixth and seventh rib near the costo-chondral junction nodules about one inch in diameter could be easily palpated. A larger nodule could be felt in the eighth rib at the costo-chondral junction and another on the ninth rib. The abdomen was held with considerable rigidity. Percussion of the liver indicated a border two fingers below the costal margin. The spleen could not be palpated. Motion of the hip, when sudden, caused exquisite pain. By care, however, it was possible to flex and to extend both the leg and the thigh. There was no localized tenderness in the pelvis or leg.

The story of prostatic involvement led to a very careful examination with negative results. Other places likely to cause osseous metastasis, the breasts, the thyroid and the kidney regions, were searched in vain. The urine showed a trace of albumin, with hyaline, granular and cellular casts. Bence Jones protein was found in

large amounts varying on different examination between 2.5 and 8 grams. There was a marked secondary anemia, with 2,500,000 red blood cells and 37 percent of hemoglobin. The white blood cell count was most interesting, 10,200 leucocytes were found. An extremely careful differential examination revealed only 42 percent of polymorphonuclear neutrophils, and 16 percent lymphocytes, but 17 percent of myelocytes, and 6 percent of myeloblasts. During the count five megloblasts and one normoblast was seen. Some cells which resembled plasma cells were seen.

X-ray examinations showed numerous dark, punched-out areas in many bones with localizations in the ribs, humerus, vertebrae and skull. The patient was told that he had a serious disease of the bones and that any slight indiscretion in lifting or any strain might cause a fracture. He was particularly cautioned to be careful of his right arm, in the humerus of which was seen a large rarefied area. Shortly after his admission, there occurred an accident so characteristic that it may perhaps be recited. A telephone call came for the patient. The nurse handed him the telephone from the bedside table, telling him that he could leave it in his bed when he finished and that she would place it back on the table for him. A slight delay occurred. The patient becoming restless placed the telephone back on the table with his right arm. The act was accompanied by a frightful pain in the middle of his arm where a fracture was later found. This accident had a most unfortunate effect on the patient's morale. Following it he ate

poorly, lost weight rapidly, until on July 8th when he finally died he presented a most extreme emaciation. Only one development of importance was observed. His white cell count increased to 21,000 and the high percentage of myelocytes remained almost unchanged. The autopsy revealed in addition to the extreme emaciation, masses and fractures of five of the ribs, a large nodule on the left humerus, a complete fracture of the right humerus, rarefactions of the skull, metastases to the liver and to both kidneys. The microscopic examination showed that the tumors in the bones were composed of cells of the plasma-cell type, together with abnormal forms of multinucleated cells.

The lantern slides may be instructive and illustrate some of the chief features of the case.

(1) The first represents an X-ray picture of the thorax. Careful inspection reveals a number of tumors and fractures. Close to the angle of the right scapula may be seen a large bulging tumor. The third rib shows for several inches almost complete absorption.

(2) The second slide shows the characteristic lesion of the skull with the sharp punched-out edges of the tumors.

(3) The next slide shows the original appearance of the right humerus. It was this picture which induced us to tell the patient that he was in imminent danger of breaking his right arm.

(4) The next slide shows a pic-

ture taken shortly after the fracture had occurred. As in many cases of pathological fracture the presence of tumor tissue tends to hold the bones in correct position. In this instance the displacement is very slight. The interne who saw the patient immediately after the accident, tried to obtain crepitus or signs of displacement and failing to find these signs he thought that the arm was not broken. It was only the continuance of excruciating pain which led to the X-ray examination and to the splinting of the arm. It is also interesting that attempts to set the arm resulted only in increasing the displacement.

(5) The next slide shows the condition found at autopsy, the over riding, the displacement of fragments, the non-union and the beginning of callus formation. In this picture also one can see the extent of involvement, the large tumor masses and the erosion of the cortex.

(6) The next slide presents a microscopic picture of the tumor cells. This particular section was taken from one of the rib tumors and shows the plasma cells closely packed, surrounding one of the large multinucleated cells which were characteristically found in all of the lesions.

(7) The next slide is a much higher power, showing the general character of the cells.

(8) The next slide shows the plasma cells infiltrating the tissues about the kidney tubules. In no place were there gross tumors in the kidneys. The infiltration, however, was dense and extensive and involved the

interstitial tissue just beneath the cortex.

(9) The last slide shows the extensive infiltration of the sinusoids of the liver.

Consideration of this case suggests several interesting questions. Early descriptions of myeloma and, indeed, some later ones considered it to be a disease strictly localized to the bone marrow. Differentiation from other tumors was often made on this basis. As case reports accumulated, it was found that, under certain circumstances, the cortex of bone might be eroded. Local extensions into surrounding tissues were described. Later cell accumulations similar to those of the bone marrow were discovered in the liver and spleen. This did not seem so extraordinary in a disease which, by definition, involves blood producing tissue. It is well known that in fetal life, liver and spleen have properties of blood formation. By many, these infiltrations have been regarded simply as extensions into the blood forming tissue of the internal organs. This conception, however, can no longer suffice. Reports have gradually accumulated concerning cases in which the invasion was not limited to the hematopoietic organs. In Frankl's case there was involvement of one adrenal gland and one ovary, as well as both kidneys. Schultz found infiltration of a tonsil. Verebely found a plasma cell tumor in the tissue about the cricoid cartilage. In three of our own cases there have been involvement of the internal organs. In one of these, a unique case which has not yet been reported, we have found wide-



spread involvement of both lungs with the production of a pulmonary and subcutaneous emphysema. Possibly the most extensive spread of multiple myeloma occurred in a case reported by Nichol in a recent number of the Canadian Medical Association Journal. The tumors of bone, in his case, were typical. Bence-Jones protein was present. The metastases included the interstitial substance of the heart, the pleurae, the pancreas, the ovary, even the Peyer's patches of the intestines and the mesenteric lymph nodes. There were, as in one of our cases, multiple nodules in the skin. The present evidence, seems to indicate that multiple myeloma may be a general disease, arising no doubt in bone marrow but involving in its course many other organs. The manner of these distant involvements resembles less the ordinary metastasis than the cellular infiltration of the leukemias.

In this connection, it may be of interest to inquire how far the comparison between multiple myeloma and the leukemias may be carried. It is often stated that in myeloma, a normal blood count is found. In our case, there is a leucocytosis with a great number of myelocytes and many myeloblasts. While this is not usual it is by no means an isolated observation. Myelocytes have been reported in other cases. In one instance these cells constituted 25 percent of the total. Plasma cells have also been demonstrated in the circulation. It might be mentioned that this represents simply an extension of abnormal cells from the diseased bone marrow. A suggestion which gains force when it is remembered that very occasionally a leukemic

blood picture has been seen in metastatic carcinoma of the bones. The similarity between the two conditions, however, does not entirely end with the blood picture. The so-called metastases of myeloma may be more accurately described as "infiltration" and resemble closely both in distribution and character the infiltrations of leukemia. Thus they are found more commonly in the liver and the spleen but may involve the kidneys, the skin and many other organs. The bone marrow ordinarily appears quite different in the two conditions. Tumors are undoubtedly rare in leukemia.

In the case of Moore, which was reported from our Hospital, there were, however, multiple bone tumors resembling most closely multiple myelomata. The clinical picture was that of myelogenous leukemia and the white blood cells at one time numbered 300,000. It is true also that in certain unusual cases of myeloma the involvement of bone marrow may be as diffuse as in typical leukemia. As an additional point of similarity, it is interesting to recall that in the case of leukemia reported by Askanazi, Bence Jones protein was found in the urine.

In this short paper it is not desired to advance a thesis that leukemia and myeloma are different expressions of the same disease. It may, however, be not entirely superfluous to emphasize that in the light of more recent reports their similarity is often most suggestive.

#### SUMMARY

1. A case of well-established multiple myeloma (Kahler's disease) has been reported.

2. This was found at autopsy to present evidence of extensive involvement of liver and kidneys. It showed during the entire time of observation a leukemic blood picture.

3. These observations are in accord with recent reports in the literature which seem to indicate that myeloma is not confined to the bone-marrow but may be a systemic disease with generalized manifestations. Also that the

similarity of multiple myeloma and leukemia is much more striking than was formerly thought.

4. The case reports of multiple myeloma have not been sufficiently numerous to bring out all the points of its natural history and further observations of its general character, its metastatic qualities and its relation to the leukemias are needed.

# Studies in Blood Volume with the Dye Method\*

By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D., *Division of Medicine, Mayo Clinic and the Mayo Foundation, Rochester, Minnesota*

NEW conceptions concerning blood are urgently needed in medicine, since the routine count of blood cells and the determination of the hemoglobin relate entirely to the concentration of the blood and are in no way related to the important problem of blood quantum. During the last fifteen years we have learned much from the accumulated evidence of studies of blood and plasma volume with the dye method. The results of these studies are now being assembled in monograph form. In this report, we shall present only a brief synopsis of some of our observations in this important but neglected field.

The dye method of determining plasma and blood volume was introduced in 1915 by Keith, Rowntree and Geraghty. The method involved a new principle: the direct introduction into the circulation of a known amount of a nontoxic, slowly absorbable dye which remains in the plasma long enough to mix thoroughly and to permit the determination of its concentration in the plasma colorimetrically by comparison with a suitable standard mixture of dye and serum. The extent of the dilution of the dye determines the plasma volume. The total blood volume is computed, utilizing for the purpose the hematocrit values

obtained after rapid and complete centrifugalization.

It was shown that for normal man the plasma volume was approximately 5 per cent of the body weight (a variation of from 40 to 60 c.c. for each kilogram) and the total blood volume 8.8 per cent of body weight (a variation of from 70 to 100 c.c. for each kilogram). Duplicate determinations on normal subjects yielded approximately identical values. Decreased volume following rapid bleeding and increased volume immediately incident to infusion by sodium chloride solution were fairly accurately reflected by this method. Increased volume relative to body weight for blood and plasma were encountered in the late stages of pregnancy and decreased volume in obesity. Changes in blood volume did not appear to bear any significant relationship to hypertension.

During the last decade the method has been employed by numerous investigators both clinically and in animal experimentation, and it has been subjected to rather searching criticism. Certain steps in the method have been questioned and changes in technic suggested. Other substances, dyes, or

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\*Read before the American College of Physicians, New Orleans, La., March 5, 1928.

colloids have been advocated as substitutes for vital red, but the original dye appears to have survived. As a matter of fact, the dye method appears to constitute the most practical clinical procedure now in use for determining the circulating plasma and blood volume. One explanation of this status of the method is that the carbon monoxide method, its only true competitor in the practical clinical determination of blood volume, has also been subjected to criticism. We have carefully considered the claims made for the latter method, and the criticism against it by various workers and can see no good reason for combining it with the dye method as has been suggested. In fact, after many years of experience with the dye method, in which approximately 1,000 volume determinations have been made on several hundred persons in health and disease, we find it sufficient for clinical needs. The particular objections that have been made to the method refer largely to blood volume; all workers concede that it furnishes the most accurate information available concerning plasma volume.

The objections which have been made to the dye method may be listed as: (1) lack of availability of vital red, (2) adsorption of dye by the blood cells, (3) variations in the time of mixing, (4) uneven distribution of blood and plasma in the body, (5) the fact that exercise is essential to proper mixing of dye in the blood, (6) indicator properties of Congo-red, (7) untrustworthiness of hematocrit data, (8) attendant dangers, and (9) the shrinkage of red blood cells resulting from the use of dry oxalate.

The various objections have all been subjected to careful consideration and to controlled experimentation. As a result we believe that all but the first and the last may be disregarded. Congo-red serves as an excellent substitute for vital red. The shrinkage in the cells incident to the use of dry oxalate as an anticoagulant averages approximately 3.4 per cent and can be readily adjusted by a change in the technic or by making the necessary correction. Our views in regard to these objections may be summarized as follows: We believe that vital red is entirely satisfactory for the determination of blood volume. It is non-toxic, nonirritant locally, and is adequate from the standpoint of slow absorbability and of tinctorial properties. It is not, however, generally available, hence, a substitute is desirable. According to Harris Congo-red has proved equally satisfactory in several hundred determinations. Many other dyes have been suggested, and there will doubtless still be others for, as we have advocated, any dye combining certain properties will probably answer the purpose. Corroboration of this is found in the work of Evans and Whipple, who used about thirty dyes, all of which yielded values for blood volume of the same order of magnitude. Colloids other than dyes may likewise suffice as evidenced by the work carried out with gum acacia.

Because of Lindhard's criticism of Congo-red as a substitute it has been subjected to control experimentation. In the concentrations used in the test there is no evidence of significant adsorption of Congo-red by the red blood cells. Variations in the dye

probably explain Lindhard's results. Neither was Congo-red detrimental because of its properties as an indicator since variation in color does not affect the method as employed. Our determinations throughout concern basal blood volume from determinations made in the morning following sleep, and with the patient at rest. If it is true, as has been suggested, that blood volume is affected by exercise, then we are faced by a new problem: the quantitative effects of exercise. However, Whipple in his study of this problem in dogs found that "no maintained or constant effects on plasma volume could be demonstrated." The opinion of Lindhard that blood volume values are acceptable only during and immediately after exercise is not borne out by our studies. For the dye method Lindhard advocates vital red as the most satisfactory test substance. Because of difficulty in obtaining this dye, we are utilizing Congo-red, and find it a satisfactory substitute.

The determination of blood volume should be made from three to six minutes after the injection of the drug. Much discussion has centered on the question of mixing curves and the most propitious time for making the determination. Two factors must be kept in mind: the thorough distribution of the dye throughout the body, and the collection of the blood-dye mixture prior to any great loss of the dye from the plasma. A consideration of the evidence the literature afforded, with the results of our own statistical observations on the mixing curves obtained in a large series of cases, did not disclose evidence that would change our original opinion, and hence

we see no reason for departure from the technic as originally outlined.

Uneven distribution of red blood cells in plasma in different vessels has not, we believe, been proved to be a serious source of error in the method. Since, in our routine work, the dye has been injected into the veins of one arm and collected from the veins of the other, our results are at least comparable. In a certain series of cases blood was collected simultaneously from the veins of both arms with practically identical results. The technical and mechanical difficulties of repeating Lindhard's attempt to collect blood from the veins of the feet are, we believe, sufficient to vitiate the results of the test and to explain in part if not in full, his discordant results.

The hematocrit values as obtained by the method are not subject to great inaccuracy. The mean variation from the average value in each of 133 quadruplicate determinations was 1.5 per cent of the total blood in the hematocrit tube, which for a practical biologic test cannot be considered excessive.

Whipple's criticism of our technic relative to the shrinkage of red cells resulting from the employment of dry oxalate as an anticoagulant, is basically sound. He claimed that in a large series of determinations by the dry method and by his method, which involves the use of 2 c.c. of 1.6 per cent solution of sodium oxalate for 10 c.c. of blood, showed a discrepancy of practically 3 per cent. Control experiments which utilize heparin intravitaly also show that the wet sodium oxalate method yields more accurate results. We are, therefore, accepting

Whipple's criticism and are making the necessary correction.

The dye method is entirely safe. We can see no justification for the fear of toxicity. During the course of five years we have not seen an untoward effect from the employment of the method in hundreds of determinations in practically all types of disease. The unfavorable results recorded would seem to be due either to unsatisfactory dyes or to faulty intravenous technic.

Blood volume may be correlated satisfactorily with body weight or body surface. Dreyer has claimed that it is a function of body surface. This is substantiated by a statistical consideration of our estimations for men and women of approximately normal body fluid. While from a scientific point of view blood volume probably should be expressed in terms of surface area, in practice values expressed in terms of weight appear to have approximately the same significance. The results of our studies are expressed both in terms of body weight and of body surface. Clinically, no advantage will accrue in the conversion of volume of blood to weight of blood unless such conversion is based on actual specific gravity determinations.

The normal values for plasma and blood volume have been determined in fifty healthy adults (preponderantly males) most of whom were men and physicians of the staff or laboratory assistants. The mean normal blood values with their probable error are as follows:

Plasma volume	{	50 = 0.5 c.c. for each kilogram of body weight
		1929 = 53 c.c. for each square meter of body surface
Blood volume	{	89 = 0.6 c.c. for each kilogram of body weight
		3383 = 33 c.c. for each square meter of body surface
Cells by hematocrit 42.1 = 0.3		
Hemoglobin 16.6 = 0.2 gm. per cent		

It would appear, therefore, that the blood volume by this method represents approximately one-eleventh of the body weight instead of the traditional one-thirteenth established by Welcker. The plasma accounts for one-twentieth of the body weight. A man of 70 kg. has slightly more than 6 liters of blood and 3.5 liters of plasma. These figures represent mean values. The range of normal is, of course, also important. It shows considerable latitude as:

Plasma volume	{	from 40 to 60 c.c. for each kilo- gram in 95 per cent of cases
		from 1600 to 2400 c.c. for each square meter in 97 per cent of cases
Blood volume	{	from 80 to 100 c.c. for each kilo- gram in 86 per cent of cases
		from 3000 to 3800 c.c. for each square meter in 88 per cent of cases

The question might be asked legitimately: Why are there variations of this magnitude in health? It cannot be answered completely at present because of lack of exact data. However, it is not excessive if compared with the range of variation in the erythrocyte count and hemoglobin values or the basal metabolism of normal persons. In seeking an explanation, how-

ever, certain factors might well be considered: (1) normal subjects show a wide range of deviation from the mean standard weight for age and height; the variations are not sufficient to classify as obese or definitely underweight; (2) age is important in the first three years of life; information is lacking with regard to subjects in the later decades; (3) certain variations in the cell volume have been noted with regard to sex; (4) rest and exercise; (5) environmental temperatures, seasonal and geographic variations; (6) diet, and (7) body temperature. Only the influence of the first factor has been adequately studied in our series. Further studies are necessary to determine the exact effects of the other factors on the volume of the blood and plasma. The mean values for the strictly standard weight group for age and height and the deviations resulting from underweight and overweight "normal" subjects are as follows:

Plasma volume	{	Standard weight 51.3 c.c. for each kilogram, 1979 c.c. for each square meter
		Underweight 53.0 c.c. for each kilogram, 1915 c.c. for each square meter
		Overweight 46.0 c.c. for each kilogram, 1992 c.c. for each square meter
Blood volume	{	Standard weight 88.7 c.c. for each kilogram, 3461 c.c. for each square meter
		Underweight 91.8 c.c. for each kilogram, 3273 c.c. for each square meter
		Overweight 78.6 c.c. for each kilogram, 3261 c.c. for each square meter

The standard group were all within 10 per cent of the accepted weight for height and age while the substandard groups represented healthy persons with variations in excess of a 10 per cent from the strictly normal range, but they were neither emaciated nor obese. The differences in body build in healthy persons have considerable effect on the plasma and blood volumes on the basis of weight, but according to surface area the relative values are more constant, especially in plasma volume.

surface area It is apparent, therefore, that several factors must be taken into consideration in interpreting volume changes in health and in disease. Incidentally, so far as body build is concerned, blood and plasma volume are essentially functions of body surface.

Repeated determinations on nineteen normal subjects at intervals of from two weeks to seventeen months showed fairly stable values for the blood and plasma for the same person. Some variations are noted, but in eight instances the changes were less than 5 per cent and in nine others they did not exceed 10 per cent. This leads us to believe that blood and plasma fluctuate somewhat from time to time but within narrow limits. The consistently high and low values respectively in certain persons seemed to increase materially our confidence in this method.

NOMENCLATURE

In the beginning of our work the lack of a suitable nomenclature for blood volume states materially increased the difficulty of interpretation

and presentation of results. So serious was this difficulty that we were impelled to create new terms in order to meet the situation. The following was suggested: "normovolemia" to indicate normal volume, "hypovolemia" to indicate small volume, and "hypervolemia" to indicate increased volume.

Obviously the ratio of cell volume

erale academic interest but of little clinical significance in actual practice. This, however, is not the case. The material thus far presented (a study of more than 250 patients) constitutes an essential background to the proper understanding of our results in the application of studies of blood and plasma volume in clinical medicine.

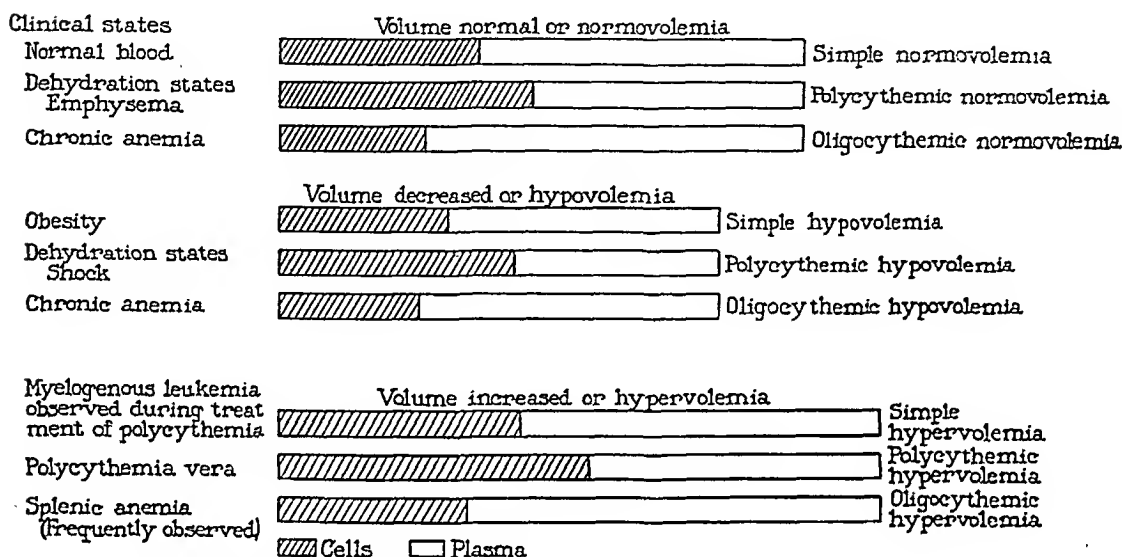


FIG. 1. Diagrammatic representation of possible blood volume states with different cell to plasma relationships.

to plasma volume is important and should be recognized in any new terminology, hence the term "simple" to represent the normal ratio, "oligocythemia" to indicate decreased cell to plasma volume, and "polycythemia" to indicate increased cell to plasma volume. These three possible relationships apply equally well to normal, increased or decreased volumes of blood, thus we have the nine volume states which are indicated in Figure 1.

#### CLINICAL DATA

From the preceding it might appear that these studies are of consid-

#### OBSITY

Twenty-seven cases of obese patients have been studied. The mean weight was 106 kg., the mean increase in weight for the group over the normal mean weight was 56 per cent. This was accompanied by an increase of only 14 per cent in surface area, of 15 per cent in plasma volume, and of 9 per cent in blood volume. Obviously the increase in volume of blood and plasma correlates better with the increase in surface area than with the increase in weight.

The obese patient (106 kg.) has approximately 500 c.c. more blood than



normal. For each kilogram of weight the blood volume has diminished from 89 to 61 c.c. and the plasma from 50 to 36 c.c. Fat obviously has a very poor blood supply. The increase in weight, although enormous, is due to fat and is not accompanied by a significant increase in blood or plasma. Increase in the volume of blood so often alleged to be the cause of cardiac hypertrophy and myocardial insufficiency in obesity is nonexistent, and hence in no way responsible for this frequent complication.

The percentage distribution of blood and plasma volume to body weight in normal and obese subjects is shown in Figure 2. Overlapping of the curves is almost entirely lacking. On the other hand, if the percentage distribution is compared to body surface, overlapping is striking, the curves showing a decided tendency to correlate (Fig. 3). Hence, in obesity, as in basal metabolism, blood volume should be considered in relation to surface area rather than to weight.

The data relating to obesity and to the new-born infant furnish the most significant basis for considering volume relation to surface area rather than to weight. In adult subjects of normal weight, and in patients suffering from most diseases it is not a matter of so great importance.

### EDEMA

The volume of blood and plasma has been carefully studied in a series of thirty-four cases of different types of edema. Obviously in order to obtain data of value it is necessary to consider blood volume values in rela-

tion to the body weight excluding the weight due to edema. This has been attempted in all cases, the normal weight being that prior to the onset of edema or the weight following edema. On this basis the following facts were noted:

The blood picture in glomerular nephritis is entirely different from that in nephrosis. In glomerular nephritis the blood volume is low with a mean value of 75 c.c. for each kilogram of body weight. The plasma volume, on the other hand, is unaffected. The decrease in blood volume is due to an absolute decrease in the volume of cells and indicates true or actual anemia; this is disturbing to the older conception that the anemia in nephritis is due to dilution from increased amounts of plasma. In contrast, the blood volume picture of nephrosis is of a moderate increase in the blood volume of both cells and plasma. In the presence of anemia there is a decided increase in plasma volume, an average of 70 c.c. for each kilogram instead of 51 c.c. noted in five cases of nephrosis without anemia. In the edema of glomerular nephritis erythrocytes are lost and little or no attempt is made to maintain volume by substitution of plasma. On the other hand, the restoration of plasma volume is complete in the case of nephrosis with anemia. Dilution of the blood suggests a possible mechanism for the production of edema and of anemia in the latter.

Cardiac edema is accompanied by blood volume changes simulating those described by Bolton in experimental passive congestion, namely an increase in both blood volume and cell volume,

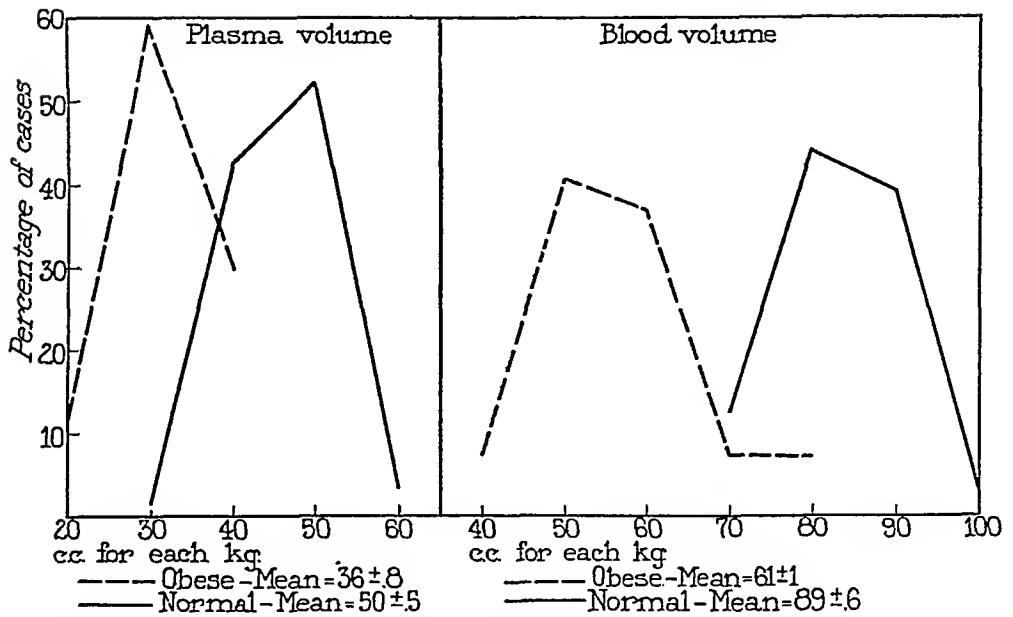


FIG. 2. Percentage distribution of relative blood and plasma volume in normal and obese subjects on the basis of body weight.

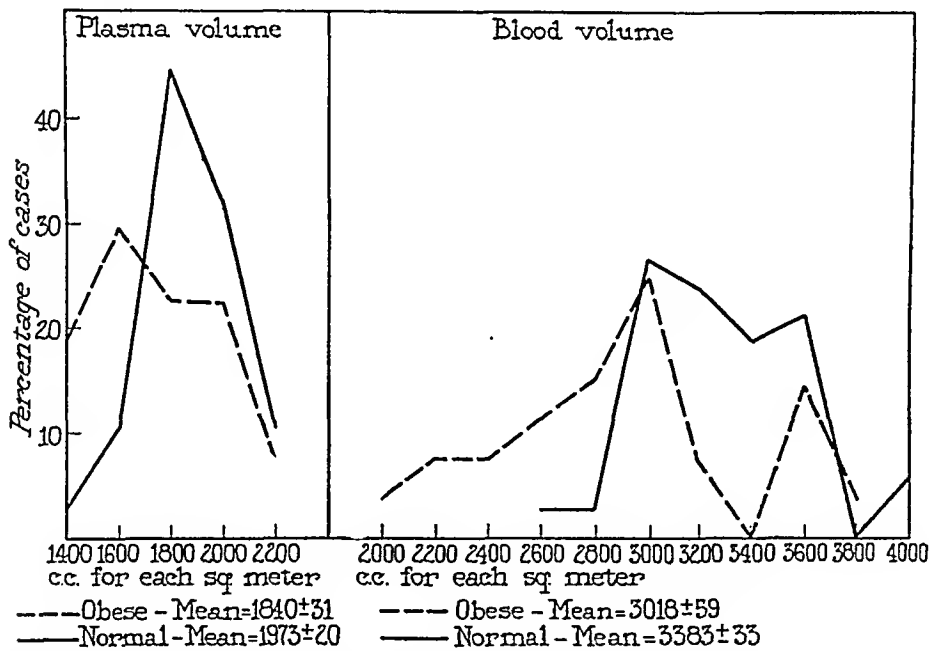


FIG. 3. Percentage distribution of relative blood and plasma volume in normal and obese subjects on the basis of surface area.

a condition of "simple hypervolemia." This is probably a compensatory reaction to secure a larger amount of circulating blood. In the edema of diabetic patients on alkaline treatment the blood picture was normal.

We may encounter degrees of edema in the presence of decreased blood

flect changed relationships in the fluid balance between the tissues and kidneys.

#### DISEASES OF THE BLOOD

The diseases of the blood offer definite contrasts (Fig. 4). The smallest volume is found in pernicious anemia.

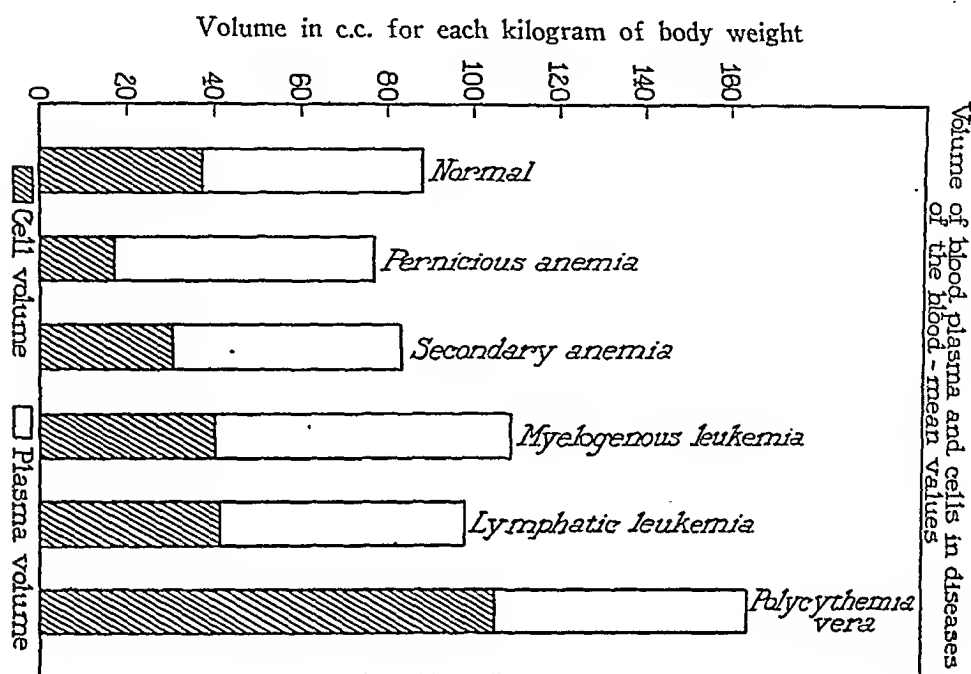


FIG. 4. Volume of blood plasma and cells in diseases of the blood, mean values on the basis of body weight.

volume and normal plasma volume (glomerular nephritis), increased blood volume and increased plasma volume (nephrosis dilution?), increased blood volume with normal cell and plasma volumes (cardiac congestion), or normal blood volume and normal plasma volume (diabetic edema).

Obviously the blood can present only one of several pictures concerned. Its rôle would seem to be passive rather than active in the production of edema. It seems more than likely that the blood volume changes simply re-

In this the decrease in cell volume is striking but the loss is partly compensated by an increase in plasma volume. Decreased volume is also found in secondary anemia with plasma replacement about the same as obtains in primary anemia. Blood volume increases in both splenic and lymphatic forms of leukemia, high values being found for both plasma and cells. In polycythemia vera, on the other hand, there is a tremendous increase in red cells and blood volume with only a slight increase in plasma volume,

which, in itself, indicates the clinical need of studies of blood and plasma volume.

#### COMMENT

The increase in plasma, although striking in many diseases, has never entered into clinical conceptions of disease. Large plasma volume is noted in splenomegaly, splenic anemia, cirrhosis of the liver, hemolytic jaundice and leukemia, and a very low value in myxedema. Obviously more should be known fundamentally and clinically about plasma. Is plasma merely a vehicle for red cells? Is it not as important, if not more important, than erythrocytes in the supplying of metabolites to tissues and cells and in the

removal of waste products? Is it a fluid tissue? Is it of itself subject to disease aside from disease involving the red and white blood cells or is it a mere passive fluid used in transportation? These and many other aspects of the plasma problem await investigation.

Finally we may group certain diseases according to whether they are characterized by increase or decrease in blood volume. In Table 1 are shown examples of diseases with a low volume of blood according to body weight. In Table 2 are listed the diseases in which there is an increased volume of blood for body weight. Finally Figure 5 indicates the values of blood volume, plasma volume and

Table 1

#### SMALL BLOOD VOLUME STATES\*

Status	Cases	Blood volume, c.c.	Plasma volume, c.c.	Cell volume hematocrit	Comment
Normal	62	89	50	42	Simple normovolemia
Obesity	27	61	36	40	Simple hypovolemia
Myxedema	10	70	48	34	Oligocythemic hypovolemia
Anemia					
Secondary	17	82	52	31	Oligocythemic hypovolemia
Primary	9	77	60	23	Oligocythemic hypovolemia; Plasma replacement
Edema					
Glomerular nephritis	12	75	52	30	Oligocythemic hypovolemia
Surgical shock	30	66 60		30	Oligocythemic hypovolemia critical level (Keith)
Dehydration dogs	10	70	35	45	Polycythemic hypovolemia (Keith)

\*According to body weight: Average values

Table 2

## LARGE BLOOD VOLUME STATES\*

Status	Cases	Blood volume, c.c.	Plasma volume, c.c.	Cell volume hematocrit	Comment
Normal	62	89	50	42	Simple normovolemia
Cirrhosis of liver	9	98	66	34	Oligocythemic hypervolemia
Banti's disease	16	98	68	30	Oligocythemic hypervolemia
Nephrosis	9	95	60	38	Oligocythemic hypervolemia
Diabetes insipidus	1	103 111	56 54	34 34	Five liters of water a day Oligocythemic hypervolemia Twenty liters of water a day
Water intoxication; dogs	30	104	64	37	Oligocythemic hypervolemia
Pregnancy	11	96	58	42	Simple hypervolemia
New-born infant	45	147	54	50	Polycythemic hypervolemia resulting in hemolytic jaundice
Polycythemia vera; after treatment with phenylhydrazine	39 5	164 90	59 60	62	Polycythemic hypervolemia Oligocythemic normovolemia

\*According to body weight: Average values

hemoglobin in polycythemia vera and the changes incident to treatment by phenylhydrazine. The decrease in the blood volume, number of erythrocytes, and percentage grams of hemoglobin are fairly parallel.

## SUMMARY AND CONCLUSIONS

It is our opinion, based on a careful and protracted study of blood volume in disease states that the changes in volume of blood and plasma are just as definite and significant as changes

in concentration. The latter are determined only as a routine, that is, the determination of hemoglobin and the count of red cells. The former, the volume of blood and plasma has been entirely neglected in medical practice.

The dye method of estimating blood volume as originally introduced is sufficiently accurate for clinical purposes and is entirely free from danger. We believe that changes in blood and plasma volume are of sufficient clinical value to warrant the adoption of this

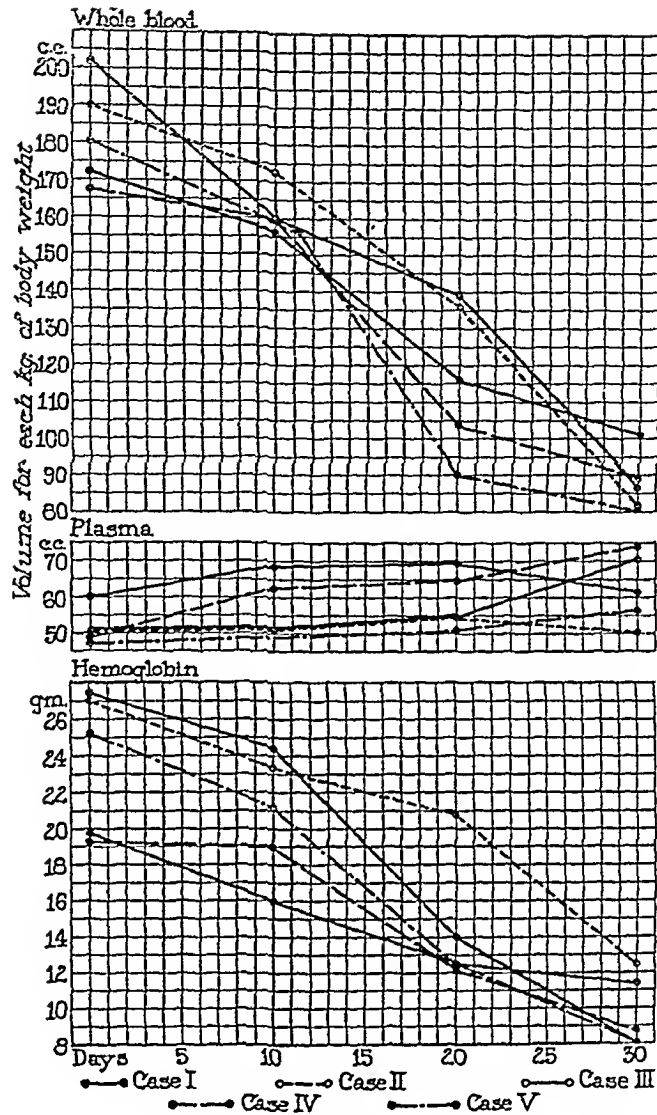


FIG. 5. Polycythemia vera. Reduction of blood and plasma volume and hemoglobin during treatment with phenylhydrazine hydrochloride.

study in clinical medicine. The true nature and significance of blood changes in disease cannot be fully appreciated or explained until a more

complete study of the blood is undertaken clinically. The dye method offers an excellent approach to this investigation.

# Cardiac Conditions Contra-indicating the Use of Digitalis\*

BY JOSEPH SAILER, M.D., *Philadelphia, Pa.*

IN the reading of medical literature and in the practice of medicine, particularly if, as a result of hospital and consultation work, one is thrown much in contact with other physicians, one is impressed with the belief that exists in the efficacy of digitalis in all forms of heart disease. Heart-disease is by no means a uniform condition. Although the symptomatology does not vary so greatly, the conditions underlying these combinations of symptoms represent pathological conditions that differ fundamentally. It has seemed, therefore, worth while to make some attempt to discover whether there is any real basis for the profound faith in the efficacy of digitalis, or whether we should attempt more or less completely to differentiate the different forms of cardiac disorders, and to attempt to discover at the present day some appropriate treatment. From the standpoint of therapeutics, it is difficult to classify heart-disease; but as it is necessary to have a working basis, I am going to attempt some rough grouping which is as follows:

First, defects in conduction. These include all forms of heart-block, bundle block, arborization block, fibrillation, flutter, and probably there should be included among these the different varieties of auricular and ventricular

premature contractions; because, indeed, the rhythmical conducting system is disturbed. Somewhat akin to these are disturbances in rhythm, particularly the paroxysmal tachycardias and nodal rhythm. Also akin to these are those disturbances which are due to conditions outside the heart, such as hyperthyroidism, infections, effort syndrome, and cerebral disturbances.

Then, and by no means entirely separate from some of the preceding conditions, we have inflammatory disturbances of the heart. These include acute endocarditis, acute pericarditis, and acute myocarditis,—the latter rather a curiosity.

Chronic valvular disease, and I have been much impressed, as have many others, with the desirability of differentiating the effects of the different valvular lesions, at least from the standpoint of treatment; chronic obliterative pericarditis; the heart of old age, or, as Cohn prefers to call it, the heart of senescence.

Finally, there is a large group of congenital forms of heart-disease, concerning which we know comparatively little, and for the treatment of which we have still less knowledge.

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\*Read before the American College of Physicians, March 5, 1928, New Orleans, La.

The object of this paper is not to give definite statements regarding the desirability of particular forms of treatment, with reference to their advantage or disadvantage. The chief object is to propound questions to which I have not hitherto been able to secure satisfactory answers.

Cushny has been much impressed by the lack of intelligence in the use of digitalis. He states that disease of the heart was treated with digitalis almost without any attempt being made to notice whether it was equally efficient in all the conditions included under this heading, and without any satisfactory observation of the effect on the pulse. He believes that there was no progress in the use of digitalis during the entire 19th century. One of the reasons for this has been the inadequacy of our knowledge of the physiological action of the drug. To quote Cushny again, it is still undetermined whether it acts as a stimulant or a sedative, and without a clear knowledge of this point, its use must still remain empirical.

What is actually known of the action of digitalis is curiously little, when one contemplates the enormous number of experiments that have been made and the vast amounts of literature that has resulted from them, not to consider the various therapeutic expositions and the attempts made to learn something definite by clinical observation.

We know that digitalis slows the heart's action, and that it does this by acting upon a brain center, presumably in the medulla; that the result of this action is transmitted along the vagus nerves to the heart. This slow-

ing consists in a lengthening of the A-V interval, and a prolongation of the diastolic interval. We know, further, that each contraction of the heart under the medical action of digitalis is strong, but that the total work of the heart is not necessarily increased, because there are fewer contractions per minute.

The effect of lethal doses need hardly be considered. The auricular contractions are variable; the ventricle may intermit, and the auricle may cease to beat. Perfusion of the excised heart with Ringer's solution to which digitalis has been added gives rise to variable results. The slow pulse may be relieved by the application of atropin. An interesting experiment has been performed by severing the turtle's heart from its body, the only connection remaining being through the vagus nerves. If then the turtle's head is perfused with digitalis, the pulse is slowed in the usual way, showing that local action is not essential.

With massive doses, heart-block occurs. It may occur in human beings to whom excessive clinical doses have been administered, as well as in animals, the first manifestation being the prolongation of the P-R interval, and then the complete dissociation between the auricular and ventricular beats. The toxic stage causes a great increase in the number of spontaneous beats produced by pacemakers in various parts of the heart. Digitalis may cause both auricular and ventricular fibrillation, the latter, of course, usually fatal.

In the laboratory it is very easy to demonstrate an increase in the blood-pressure after the administration of digitalis. It is much more difficult to



show that this is accomplished by therapeutic doses, and, indeed, it is questionable if therapeutic doses can increase the pressure in so-called essential hypertension. Other undesirable actions of digitalis are vomiting, colic and diarrhea,—possibly all of them central; and it is even at this late date undetermined exactly what is its effect upon the kidneys.

Nevertheless, there will be no disagreement, I think, that digitalis is of the utmost value in many forms of heart disease, even although the method by which it produces improvement is not known. In discussing the effect of digitalis upon defects in conduction, I shall take it for granted that the administration of digitalis in digitalis heart-block is necessarily bad. There is some question, however, regarding its effect upon heart-block due to other causes. Apparently a distinction must be made between incomplete heart-block and complete heart-block. Cushny, Sollmann and all others agree that in incomplete heart-block digitalis can only do harm, inasmuch as it will change the II - III type of heart-block

$$\begin{array}{c} \text{II} \quad \text{III} \\ \hline \text{I} \quad \text{I} \end{array}$$

to a complete form. In discussing the matter with clinicians, I have been impressed, however, with the fact that sometimes digitalis can do no harm in these cases, because the dose employed has been so small that no physiological action could be expected. Doses not exceeding 10 drops, of a possibly poor commercial tincture three times a day, are not likely to increase a partial heart-block. This is not a matter of scientific importance. It is not even a matter of rational therapeutics but it sometimes requires diplomacy to attempt to controvert the insistence of

the physician that the digitalis has apparently been of benefit, even although he has used at the same time many other measures, particularly rest. Sollmann, however, is of the opinion that digitalis may be of some benefit in complete heart-block, inasmuch as it may stimulate the idio-ventricular contractions, and in that manner increase the activity of the heart and improve the circulation. Willius, however, does not believe that digitalis is helpful in these cases, even although the auricle may be fibrillating. My own experience has not been extensive, particularly because I have always felt that digitalis was necessarily contraindicated even in complete heart-block, and that other remedies offered a better chance of producing the results that Sollmann thinks might be produced by digitalis. Recently, however, there was a case of complete heart-block in my ward at the Philadelphia General Hospital, to which my Resident administered some digitalis. I was not averse to watching its effect. The heart's action was not increased, but the regularity of the ventricular contractions seemed to be better. As this patient, who belonged to the lowest class of society, had a bed in which he could rest for twenty-four hours, was given a suitable diet of well-prepared food, and felt, probably for the first time in years, assured of his bed and board, and therefore relieved of anxiety, it is quite possible that these other factors helped as much as, or even more than the digitalis in producing the effect. As the dose was very small, 1 c.c. of an assayed tincture three times a day, it can hardly be said that it proved the harmlessness of large doses of digitalis in complete

heart-block. Bachman has reported two cases in which strophanthus was used with doubtful benefit.

Branch bundle block is a condition for which we have practically only the electrocardiograph as a means of diagnosis. It is by no means uncommon. It is generally regarded as a serious lesion, but is compatible with many years of reasonably comfortable life; and there are some atypical forms which seem to interfere not at all with cardiac efficiency. I have one patient whose electrocardiogram for over twelve years has indicated this condition. The sole disability has been an occasional attack of tachycardia. He was on the front with the A. E. F. during the late war, and is able at the present time to play thirty-six holes of golf daily for a week at a time without discomfort. The existence of such cases renders it difficult to draw definite conclusions regarding the effect or non-effect of treatment. I have found little in the literature upon the treatment of this condition. The diagnosis has apparently been the most interesting feature. On theoretical grounds, anything which would further interfere with the conduction through the heart when one branch of the bundle of His has already been seriously damaged and perhaps completely incapacitated, should be carefully avoided. Nowhere have I found a statement of any clinician that he has recommended digitalis in this condition. I have never personally used it, and therefore I cannot say definitely that it does harm. That the heart may continue to act favorably for a considerable period of time, although the severe type of branch bundle block is present, and digitalis is not given, is a

matter of general knowledge; and I shall present a lantern slide of such a case, who died of an acute infection of the lungs four years after the branch bundle block was discovered, and presumably a longer period after it had developed.

The question of arborization block is considerably more difficult. In this, usually as a result of disturbances in the coronary circulation, certain groups of the conducting fibres are thrown out of activity, and there are two factors to be considered. First, the immediate effect of the embolus in the heart. This may be rapidly fatal, or the heart may recover. The recovery may be temporary, or reasonably complete, and it is to be supposed that sometimes there is the establishment of a collateral circulation which leaves the heart in almost as good condition as it was before, with only a scar on the ventricular muscle to betray the lesion which previously existed. If it could ever be definitely proved that digitalis stimulates the heart-muscle, improves its contractility and the force of the contractions, it might well be argued that the administration of digitalis in these conditions would be a distinct advantage. However, if its effect of diminishing the contractability of the bundle of His can be shown to extend to the other conducting fibres of the heart, then digitalis might be injurious. If some sequel occurs, such as fibrillation of the ventricle, as in the case recently reported by Levine, in which the administration of enormous doses of quinidin sulphate apparently saved the patient's life, necessarily there would be some question regarding the possible utility of digitalis; but in the case which has

been mentioned, Levine decided not to employ it. Clerc and Levy report the case of a woman with myocardial insufficiency who showed slight amelioration on digitalis, then developed cyanosis, tachycardia and erythema and died in 4 days. There were found a mitral lesion and an infarct of the right auricle. Keith gave digitalis in one of these cases of incomplete bundle block with apparent benefit.

My own experience is somewhat scanty; but some of it, at least, very definite. I was asked to see a physician who had fallen upon the golf-links, suffering intense precordial pain. He was carried to the club-house, laid upon a sofa in the hall downstairs, and remained on that sofa until his death seven days later. His mind was perfectly clear. The pain was relieved by hypodermics of morphine. When I saw him on the third day, it seemed not impossible that recovery would occur. On the sixth day, his physician, feeling that he was not improving as he liked, and possibly at the request of the patient, administered some digitalis. He reported to me on the seventh day that the patient was greatly improved by this, but in less than twenty-four hours after the first dose of digitalis the patient died. No conclusion can be drawn from this. He might easily have died, whether the digitalis had been given or not; and whether as a result of his faith in the drug, or because it really gave him cardiac relief, it is quite possible that the digitalis did not contribute in any way to the fatal end.

However, I had another case in which an old woman was brought into the ward of the Presbyterian Hospital, suffering from the usual indications of

coronary thrombosis, with the characteristic changes in the electrocardiogram. For three months she remained there, apparently improving, and the object of our solicitous care, for I was very anxious to observe how long it would be possible to keep her alive. At the end of this time the service changed, and my colleague immediately commenced digitalis therapy. Her death occurred in less than forty-eight hours after it was administered, although the dose was by no means large, 20 minims three times a day, probably, as nearly as I could determine, measured by a dropper. At the autopsy the coronary circulation was filled with mercury, and an x-ray taken of the heart. This showed complete block in the anterior coronary artery. Again the results are not absolutely conclusive, for anyone with an obliterated coronary artery, even although there is apparently a fairly well established collateral circulation, must be expected to die at any time; and the digitalis may have had nothing to do with the result. But at least it can be assumed in both cases, that the digitalis did not serve in any way to prevent the fatal result. Pardee reports a case of coronary thrombosis that recovered. Digitalis was not given, so that its use is not essential to recovery.

I shall not discuss either auricular fibrillation or flutter. Both forms of block have so incontestably benefited by the administration of digitalis that they do not properly belong to this essay. Even in the fibrillation that may accompany abdominal septic infection is benefited by digitalis or quinidin according to Felberbaum and Finesilver.

Paroxysmal tachycardia is a name

used to designate several varieties of cardiac disturbances. In all of these varieties digitalis has been used. In all of them it has failed to slow the action of the heart. Whether there is some substance in the circulation which acts, as atropin does, upon the center in the medulla, and prevents its receiving the digitalis stimulation, or whether there is some other factor whose nature we cannot even surmise, in these cases digitalis can do distinct harm if pushed until it produces toxic effects. Then it is even possible that it has an injurious effect upon the brain. It is hardly worth while to continue the discussion of this form of heart-disease, because it is so generally admitted that digitalis is futile.

The same is true of nodal rhythm, in which apparently the pace-maker is dislocated to the node of Tawara, or somewhere in its neighborhood. Digitalis seems to have no effect in these cases. It does not appreciably stimulate the force of the contraction, for there is no reason to suppose that this is insufficient, nor has it any tendency whatever to restore the normal rhythm; at least I have come across no references to this. Jones and White report two cases of atrioventricular nodal rhythm in which digitalis was not given. One of the cases proved to be coronary thrombosis. It is also reasonable to suppose that coupled beats and pulsus bigeminus, as are produced by over doses of digitalis, can hardly be relieved by this drug. Conner describes an unusual type of gallop rhythm, that might occur during digitalis treatment but was not apparently caused by it.

There is more difficulty, however, in determining the value of digitalis in

the tachycardias that occur in soldier's heart, or effort syndrome, in exophthalmic goitre, in infectious diseases, and in the tachycardias of functional cerebral disturbances. The latter, I believe, are so closely akin to effort syndrome, that they may be considered together. As long ago as the Civil War, Dr. da Costa of Philadelphia found that digitalis was of no value in these conditions. The experience in the late war only confirmed and emphasized this view. Even large doses of digitalis had no effect upon the rate of the pulse, and seemed to have a very bad effect upon the patient, so that they became more nervous and distressed than they were before its administration.

Hyperthyroidism is sometimes complicated by auricular fibrillation. The majority of those who have studied this complication, such as Foster, Anderson, and others are of the opinion that digitalis is beneficial. Plummer who has had such a large experience in these cases, in a paper read before the Association of American Physicians, believed that digitalis might be injurious. At the time that paper was read, not a single physician who discussed it differed from his opinion. Nevertheless, those who believe in the use of digitalis in cases of hyperthyroidism, complicated by auricular fibrillation, have continued to report excellent results. If I may express a personal opinion, it is that the auricular fibrillation of hyperthyroidism is not as obstinate as the auricular fibrillation that occurs in mitral disease, especially mitral stenosis; that it responds fairly readily to digitalis therapy, and that after it has been relieved, the patient seems better than before. It has

not yet, at any rate, been definitely proved that digitalis, if properly employed, is injurious in selected cases of toxic goitre.

I am very loath to discuss at all the question of the use of digitalis in infectious diseases. There is no doubt that at the present day it is almost universally employed in these conditions. I do not think that I have been called to see a case of pneumonia for a long time that had not been receiving digitalis before I saw the patient. The use of digitalis in pneumonia antedates by many years the late war. Cohn gave a reason for its use, and urged it very strongly. There is no question at all that digitalis in infectious disease with tachycardia fails to slow the heart, even in large doses. The reason that Cohn gave for its use was that in pneumonia, particularly, auricular fibrillation was not uncommon; and that when it occurred, if the patient were partially digitalized, it was easy to complete the digitalization, and in this way the chance of recovery was enhanced. Stuart Hart was opposed to this view. Cushny is of the opinion that if auricular fibrillation occurs, it is time enough to digitalize the patient when it is discovered. On the other hand, it may be that partial digitalization prevents its occurrence, and that when it does appear, it is such a serious complication that there is rarely time to wait until complete digitalization is accomplished.

In an experience at Camp Wheeler, where I was stationed during the first period of my service, we had 1500 cases of croupous pneumonia. These were studied as well as possible, typed, and in many cases blood-cultures were obtained. They were all in young

men, nearly all of them in good condition, although some of the patients had recently had measles, and others had recently had attacks of the mild, early epidemic of influenza. No cases of irregularity of the pulse was noted. We had neither polygraph nor electrocardiograph, and therefore it is possible that cases were overlooked; but I do not think that I have ever worked with a more enthusiastic group of men than were the ward surgeons on the Medical Service at Camp Wheeler, and I believe that if cases were missed, at any rate our mortality was satisfactory. Very few of these patients received digitalis.

In my hospital services, where I receive many cases of pneumonia every year, where we have the advantage of using the electrocardiograph, auricular fibrillation is rarely detected, and digitalis in view of this is rarely given. It must be admitted that the administration of digitalis during the course of pneumonia, typhoid fever, or other infectious disease, has never been shown to be injurious. Some experimental evidence that digitalis may be of value in the circulatory disturbance produced by diphtheria toxin is offered by Gold. I may mention that Wyckoff and Boldring proclaim ovabain is not of much use in febrile conditions. They regard clinical improvement as the only criterion.

There is no evidence at the present time that digitalis is of any value in acute endocarditis, myocarditis, or pericarditis. Morrison in a study of 145 cases of subacute bacterial endocarditis in the records of the Massachusetts General Hospital reaches the conclusion that all treatment is futile. Neither is there any evidence that it

does much harm, although in one case that I shall mention later the distress following an attempt to digitalize the patient was rather startling. Moderate doses of digitalis in endocarditis, as in all other conditions, are practically harmless, and probably not very effective. We know too little about acute myocarditis, and it usually kills so rapidly, that the question of therapeutics rarely arises. I have had within the last five years two cases of abscess of the myocardium, neither of them suspected during life; one was a complication of a diabetic carbuncle; the other was a complication of liver abscess; and in neither patient was the serious condition of the heart recognized. Joachim and Mays report a case of calcified cardiac aneurism, in which massive doses of digitalis relieved an attack of cardiac weakness and tachycardia, but failed, as did quinine, to relieve a second attack and the patient died.

The value of digitalis in valvular disease has been a question of much dispute. There seems to be no essential disagreement among clinicians that in disease of the mitral valve, digitalis will often serve to restore compensation; when compensation is restored, digitalis aids to maintain it, and there is no evidence that, used properly, it ever does any harm. This is particularly true of mitral stenosis; and various theoretical explanations have been advanced to explain why it does so. Theoretical explanations for physical signs, or the effect of treatment in heart-disease, have usually been wrong, and therefore should be entirely avoided.

The argument was waged about the effect of digitalis in aortic insufficiency.

It is permissible to mention in this condition the explanation that digitalis, by prolonging the diastole of the heart, permitted more blood to flow back into it through the incompetent aortic valves, and actually increased the seriousness of the condition, for theoretically, it is desirable to make the diastolic pause as brief as possible, in order that more blood should remain in the general circulation. One might easily argue on the other side that the increased velocity of blood through the general circulation compensated for the small amount that could flow back into the ventricle; I mean the small amount that is compatible with cardiac compensation; for when severe decompensation occurs in aortic insufficiency, it is usually impossible to restore the heart to a compensated condition. Christian, however, and others have criticized this statement. Christian particularly finds that digitalis is quite useful in aortic insufficiency. It seems to steady the heart, to relieve the patient, and perhaps to promote diuresis, and is therefore a valuable drug. It must be remembered that mitral stenosis may be mistaken for aortic insufficiency and that digitalis naturally relieves it. Holt has reported such a case.

It will be generally admitted, I think, that in aortic regurgitation, the anti-syphilitic remedies have been of some, but very doubtful benefit; and that the most important remedial measure that we have is rest, perhaps accompanied by some forms of physical therapy. On one occasion I saw a boy of 15 years, who had a rheumatic aortic insufficiency. This had apparently occurred when he was 8 years of age. His compensation had been good, and he had

played on various athletic teams in his school, being particularly noted for his strength and quickness. He had a mild attack of decompensation following the football season; and I placed him in bed, and he made a fairly good recovery, returning to school. Within a month, however, he developed signs of acute endocarditis, which was supposed to be due to the streptococcus cardio-arthritis. During this attack the heart became steadily worse. He was treated with vaccine, which apparently had a moderately bad effect. During my absence from the city, one of my colleagues who saw him decided he was doing badly, and thought it would be worth while to attempt to digitalize him. He was therefore given in one day 8 c.c. of an assayed tincture of digitalis. He became so much worse immediately, that it was almost impossible not to regard the digitalis as having been injurious. In three days he died. He would surely have died if the digitalis had not been given. The only question that arises in our minds is, whether it might have hastened his death. It was considered that he may have had in addition to his acute endocarditis some myocarditis, and we also considered the question as to whether the results of the aortic insufficiency were made more severe by the administration of digitalis or not.

I do not know anything, nor have I been able to find anything in literature, regarding any effective treatment for congenital heart-disease. The patients that I have had, and in which I felt that I could recognize this condition with any certainty, were treated entirely by rest, although as digitalis seems more useful when right preponderance

is present than when left preponderance is present, and as all cases of congenital heart disease have right preponderance, it may easily be true that digitalis is helpful.

There are three other conditions which should properly be discussed. The first is chronic oblitative pericarditis. This depends upon the extent of the obliteration. If it is both endo- and exo-pericarditis, nothing is of much help. The heart apparently dilates, decompensation becomes severe, and the patient dies. Simple exo-pericarditis is difficult to recognize during life. It rarely gives rise to much enlargement of the heart or to much decompensation and probably never requires treatment. Endo-pericarditis may be compatible with a considerable duration of life. I had one patient with a very distinct Broadbent sign in my ward for three years, and used him for demonstration to innumerable ward-classes. His heart was very large; but the lazy life he led as a ward patient seemed to agree with him excellently; and until shortly before his death he was practically compensated. In these cases digitalis is often recommended, but there is great question as to whether it ever does any actual good. Perhaps in slowing the heart's action it diminishes the frequency of the tugs of the heart-muscle against the parietal pericardium, and may save the heart exertion. This is another of those theoretical explanations.

The heart in old age has been very much discussed. The comfort that is often experienced by physicians in administering small doses of digitalis in these old people is so great, that in the absence of any distinct evidence

of injury from the digitalis, there is no reason why it should not be given. It is very difficult, however, to prove that it does any good. Sollmann thinks that if the cardiac muscle is degenerated digitalis will be useless or even harmful because it imposes too great a task upon the remaining weakened muscle fibres.

This does not apply, of course, to the cases of auricular fibrillation in old persons, which should be treated in the same way that auricular fibrillation should be treated in all other patients. Marvin advocates digitalis in the dropsies of congestive heart failure, returning to Withington's original contention.

The use of digitalis in hypertension has also been discussed. O'Hare believes that it is never contraindicated. Cushny and Sollmann lay emphasis up-

on the fact that digitalis in therapeutic doses never increases the blood-pressure. There is therefore no reason why it should not be used; but it remains to be shown that it does any particular good. Sollmann has shown that the intravenous administration of digitalis gives rise to a fall in the blood-pressure, but this is only temporary. However, it is no more temporary than the fall which is produced by the administration of nitroglycerin; but in what way the slowing of the heart, or the impairment in cardiac conduction can help a patient who is suffering from the so-called essential hypertension, is not clear, and therefore the burden of proof, I think, at the present time rests upon those who advocate digitalis in these conditions to show how it may be of benefit.

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# Clinical and Pathological Evidence of the Influence of Iodine in the Therapy of Primary Hyperthyroidism\* †

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**A**FTER more than a century of familiarity with the isolation and identification of iodine (Coindet 1820) and a growing knowledge of its natural distribution in plant and animal life, its agency in the physiology of the latter, and man in particular, is as yet not thoroughly understood.

In the accounts of medical practices of the many centuries of the past, are records of the uses of iodine in many body ailments and especially in goiterous enlargements of the neck. Its use in the latter condition gradually became rationalized (1) by the determination of the presence of iodine as a natural constituent of the thyroid gland (Bowman 1895), (2) by the experiments of Marine and Lenhardt who protected animals (dogs and fish) from goiterous enlargements by the addition of the required amount of iodine to their food; (3) by the further experiments by these authors (Marine and Lenhardt), (1) on re-

roxin as the active principle of the thyroid (Kendall, 1914) and (5) by the observations of Plummer and Boothby concerning its clinical use in instances of hyperactivity. To these might be added many other similar experiments and studies all of which tended to point out the specific role of iodine in the physiology of the thyroid both in health and disease.

While these important advances, relative to the identification of iodine, as a positive and necessary factor in thyroid function were being made, many clinical observations were also made with a view to a better understanding of the then empirical use of iodine in thyroid dysfunction. Iodine was used in its crude form (ashes of sponge or seaweed) for many thousands of years, as a remedial agent, in so-called goiter. The purification of iodine and its compounds led to more accurate dosage and the development of various means of administration. The results

(1) MARINE, DAVID AND LENHARDT: Arch. Int. Med. 4:440 (Nov.) 1909.

generation and hyperplasia in the thyroid as influenced by iodine; (4) by the isolation and identification of thy-

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were not wholly satisfactory because of the lack of control of clinical conditions and the inability of early clinicians to accurately differentiate the different types of thyroid disease. But from the time of the establishment of Parry's disease (1786) as an entity it was considered as unwise to use iodine in the therapy of this condition. Occasionally, however, on account of erroneous diagnosis or by accident, iodine was administered and beneficial results were noted. Trousseau (2)

(2) *Clinical Lectures* 1:587, Trans. By Bazire, New Sydenham Soc., 1868.

(1863) by mistake, gave tincture of iodine instead of tincture of digitalis to a patient with a supposed primary cardiac irregularity, which was probably secondary to hyperthyroidism. Improvement of the patient was noted and recurrence of the symptoms was observed when the correction was made. Numerous other instances of the beneficial uses of iodine in so-called exophthalmic goiter were recorded, but in general the results were bad and in many of the large clinics of Europe the use of iodine in this disease fell into disrepute. But surgery, one of the oldest methods of treating goiters, was productive of a mortality rate so high in primary hyperthyroidism that frantic efforts were constantly being made to better its technic and search for further aids in the therapy of this condition. The introduction of bed rest, isolation of clinical types, the use of soporifics, and preliminary pole ligations helped to lower appreciably the mortality rate. In the meantime the effect of such partial surgical removal on the remaining gland stump

was studied by Wagner (3), Horsley (4) and Halstead (5), who found that

(3) *Wien Med. Bl.*, 7:771, 1884.

(4) *Lancet*, 2:1163, 1886.

(5) *Johns Hopkins Hosp. Rep.*, 1:373, 1898.

reconstruction hyperplasia and hypertrophy occurred. This finding led to a further understanding of what surgery accomplished besides a mass removal of offending parenchyma. It also opened the way for a study of the additional effect of iodine as a therapeutic adjunct.

Following the introduction of this and other data, iodine began to be used in small doses as a prophylactic measure. About the same time Plummer, having in mind the possible toxicity of incompletely iodinated thyroxin and the variations in the symptomatology of the clinical types, suggested that the administration of Lugol's solution in instances of primary hyperthyroidism might be of value. Subsequently Plummer and Boothby (6) published the beneficial results of

(6) *J. Iowa M. Soc.*, 14:66-73, 1924.

its use in selected cases. Similar reports by others began to appear. Starr and Segall (7) in a study of forty-

(7) *Arch. Int. Med.*, 34:355-364 (Sept.) 1924.

two cases made additional observations. These authors determined that the detoxification rate (based upon per diem reduction in the basal metabolic rate) was 3.7 points, a rate similar to that obtained by Segall and Means (8)

(8) *J. A. M. A.*, 69:33, 1917.

with sub-total thyroidectomy alone. They further pointed out, that in 48%

of these cases, iodine therapy had the same effect upon the basal metabolic rate as the removal of five-sixths of the gland; that iodine would not produce a permanency in the remission, recurrence being the rule; and that the return of intoxication would result in a much higher basal metabolic rate. They therefore concluded that no gap between iodine therapy and operation should be allowed. This conclusion was concurred in by Clute (9),

(9) J. A. M. A., 86:105-109, Jan. 9, 1926.

who regarded the "optimal time" for thyroidectomy to be within a period of two to three weeks after iodine therapy was started. During this time he observed the most marked clinical improvements and the greatest drop in the basal metabolic rate. He regarded operation within such a time limit as safe and also stressed the fact that the toxicity recurring after cessation of iodine treatment is greater than before its use, if surgical removal is not promptly instituted. He further concluded that in the severe cases iodine reduced the necessity of pole ligations from 51 to 13%, but that iodine even though administered over a long period of time does not cure exophthalmic goiter. Petren (10) regarded

(10) U gesk f. Laeger, 88:363-364, Apr., 1926. Abst. J. A. M. A., 87:77, July, 1926.

iodine as having a life saving action. He also noted that the symptoms reappeared after cessation of the treatment and recommended the use of roentgen rays and ligation as additional measures.

Marie (11) concluded that the re-

(11) Presse Med., 34:58-583 (May, 1926). Abst. J. A. M. A., 81:66, July, 1926.

sults of the use of iodine in the treatment testifies only to the fact that a disproportion exists between the iodine content and the requirement of the organism at that time rather than a deficiency of iodine. Marine (12) later (12) Ann. Clin. Med., 5:942-949, Apr., 1927. called attention to the injudicious use of iodine in too large amounts (Lugol's contains 125 mg. iodine per cc.) It was suggested by him that smaller amounts more nearly physiologic (1 mgm. daily) should be given. He spoke of "heroic doses" as a preoperative measure as dangerous, from which much harm has occurred and will continue to occur. Marine regarded the beneficial effects of iodine in Graves' disease as limited and its injurious effects as serious. He also stated that these injurious effects have increased during the last three years and are of more serious consequence, than those disturbances noted as a result of the use of various iodine containing substances as preventive measures. Marine explained the effect of iodine on the probable basis of colloid storage which holds back the secretion. He stated that when the secretion is released it is reestablished with full force and yields larger amounts, the gland becoming larger and more solid. Helwig's (13) views were in agree-

(13) Klin Wschnschrgt 5:2356-2357 (Dec.) 10, 1927.

ment with those of Marine. He concluded that iodine feeding called forth an enlargement of the follicles and a thickening of the colloid, and that in his experience the severest cases of

Basedow's disease were encountered after iodine administration.

Sager (14) in a recent study at the (14) Arch. Surg. 15:878-894, Dec. 7, 1927. Mayo Clinic again called attention to the necessity of differentiating the types of the hyperthyroidism before the use of iodine, on the basis of Plummer's views referred to above. He quotes Plummer as regarding the action of iodine as due to one of three possibilities. (1) Complete iodination of thyroxin in the tissues (possible but improbable). (2) Complete iodination of thyroxin in the thyroid (most probable). (3) Blocking of the discharge of the hormone (also probable).

From these, and many other important studies of the past we learn that the efficiency of surgery and other forms of therapy have been augmented by the knowledge of the existence of an iodinated hormone. Further that pure iodine may be advantageously used as a valuable adjunct in the treatment of instances of hyperthyroidism. This latter accomplishment is relatively new, and is far from being completely understood in spite of the excellent contributions appearing in the literature.

We therefore consider it not amiss to record the analysis of the clinical and pathological evidences of the influence of iodine therapy in instances of primary hyperthyroidism in this endemic goiter area.

The data here analyzed are those gathered from instances of primary hyperthyroidism, comprising a series of consecutive instances in a group

that constitutes about 12% of the total thyroid disturbances seen by us.

Great care was exercised in differentiating the primary forms from the types of so-called secondary hyperthyroidism. All of these patients were submitted to a combination of rest and iodine therapy, followed by operation. (Double thyroidectomy).

For the purposes of study the information concerning the 131 instances of primary hyperthyroidism was divided into three groups according to the age. Group 1, 15 to 25 years (average age 21 years); group 2, 26 to 50 years (average age 39); and group 3, above 50 years (average age 57 years). This division, while somewhat arbitrary nevertheless takes into consideration puberty and adolescence, procreation and the menopause, and the post climacteric periods in the respective groups.

The clinical data of these three groups were collected according to a plan, the object of which is to illustrate the effect of iodine administration on the subjective and objective clinical manifestations before and after its use and to correlate these phenomena with the pathological findings. Accordingly the facts were arranged under the headings of (1) Admittance data; (2) Pre-operative iodine therapy; (3) Operative; (4) Post-operative therapy; (5) Discharge record; (6) Pathological study (See charts 1 to 7 inclusive).

In a consideration of such clinical data one must keep in mind many factors that may influence the clinical syndrome ordinarily associated with hyperfunction of the thyroid. The usual characteristic symptoms such as fa-

## CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART I  
Patients Ages Ranging From 0 to 25 Years Inclusive

ADMITTANCE HISTORY										IODINE AND REST THERAPY			PRE-OPERATIVE RECORD			OP. Spec. in Gm.	POST-OPERAT- IVE I THERAPY			TIME OF DIS- CHARGE REC.			Acc. No.	
Marital Sex	State	Age	Chief Clinical Symptoms	P	S	D	B.P.	BMR	Wt.	Lugol's Sol'n			T.	P.	R.		Form	Amt	Freq.	T	P.	B		Cys. Hos.
F	S	20	Nerv. Wt. G.I.D.	114	144	80	64	55	133	3M	TID		98	113	27	50				99	94	20	9	17215
F	M	22	Exoph. Nerv. Wt. Ftg.	124	140	80	60	75	123	5M	TID	1	98	92	20		Lug- Dr. Lugl	3M	BID	98	80	20	9	17728
F	M	24	Nerv. Rpd. Ht. Enl.	135	155	80	75	28	128	10M	TID	2	98	85	22	61	Lug- Dr. Lugl	10M	TID	99	90	20	6	14126
F	M	19	Resp. Dif. Enl. Nerv. Wt. Rpd. Ht.	100	130	90	40	28	115	5M	TID	2	97	100	20	71	Lug- Dr. Lugl	10M	TID	99	95	20	9	14518
F	S	22	Resp. Dif. Enl. Nerv. Wt. Rpd. Ht.	100	124	60	64	25	114	10M	TID	6	98	95	22	62	Lug- Dr. Lugl			99	82	22	18	17224
F	S	18	Resp. Dif. 2. Enl. Exoph. Nerv. Rpd. Ht.	140	155	60	95	25	121	10M	TID	12	98	105	22	138	Lug- Dr. Lugl	4M	TID	98	95	18	19	17563
F	S	17	Enl. Exoph. Nerv. Rpd. Ht.	135	150	60	90	42	117	10M	TID	7	98	105	20	71	Lug- Dr. Lugl	10M	TID	98	95	20	14	17308
F	M	25	Rpd. Ht. Exoph. Nerv. Wt. Ftg.	110	120	70	50	42	104	5M	TID	8	95	105	22	47	Lug- Dr. Lugl	5M	TID	99	95	20	13	17569
F	M	22	C.I.D. Wt. Nerv. Res. Dif.	100	130	60	70	32	116	5M	BID	5	98	98	22	18	Lug- Dr. Lugl	3M		98	85	20	9	17715
F	S	15	Dif. Nerv. Rpd. Ht. Resp.	120	130	70	60	10	116	5M	TID	13	99	140	25	105	Lug- Dr. Lugl	5M	TID	99	102	25	12	14211
F	S	23	Dif. Ftg. Enl. Nerv. Wt. Rpd. Ht. Res.	130	150	75	75	38	139	10M	TID	5	98	100	25	115	Lug- Dr. Lugl	5M	TID	97	80	20	10	13568
F	S	24	Enl. Nerv. Rpd. Ht. Ftg.	90	130	80	50	40	110	5M	TID	3	98	82	22	27	Lug- Dr. Lugl	5M		98	80	20	12	17502
F	S	21	Dif. Enl. Nerv. Wt. Res.	120	160	80	80	35	138	10M	TID	2	98	90	20	35	Lug- Dr. Lugl	10M	TID	99	130	20	6	14047
M		22	Wm. G.I.D. Exoph. Nerv. Wt.	112				34	163	6M	TID	120	98	90	20	105	Lug- Dr. Lugl	10M	TID	97	72	20	7	14705
F	S	17	Nerv. Res. Dif. Enl.	110	120	60	60	40	130	5M	TID	4	98	80	22		Lug- Dr. Lugl			98	100	20	8	14551
F	S	25	Wm. Rpd. Ht. Res. Dif.	130	122	74	48	40	90	5M	BID	3	95	94	21	22	Lug- Dr. Lugl	1M		98	88	20	6	16335
F	M	23	Dif. 2. Ftg. Enl. Nerv. Rpd. Ht. Res.	140	148	74	74	42	119	10M	TID	10	99	130	18	135	Lug- Dr. Lugl	5M	BID	98	80	18	18	15055

KEY:-  
 CHIEF CLINICAL SYMPTOMS:- Exoph.- Exophthalmos, Nerv.- Nervousness, Wt.- Loss of Weight, Rpd. Ht.- Rapid Heart,  
 Res. Dif.- Respiratory Difficulty, 1, 2, or 3 - Degree of Res. Dif., Ankles- Edema of Ankles,  
 G.I.D.- Gastro-intestinal Disorders, Enl.- Enlarged Thyroid, Wm.-Muscular Weakness.

## CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCE OF PRIMARY HYPERTHYROIDISM

EXPERIENCED BY THE USE OF IODINE THERAPY

CHART 11

Patient's Ages Ranging From 26 to 50 Years Of Age.

ADMITTANCE HISTORY										IODINE AND REST THERAPY		PRE-OPERATIVE RECORD			OP. St. Spec In Cm.	POST-OPERAT- IVE I THERAPY			TIME OF DIS- CHARGE REC.				Acc. No.
Sex	Age	Chief Clinical Symp.	P	Syst Dia	P.P.	EMR	St.	Ami	Fre	Dur.	T	P	R			Fe.	Ami	Fre	T	P	R	Dys Hem	
F	3	30 Nerv. H'dac. Resp.Dif.	100	123	75	50	33	69	5M	SID	6	98	101	20	10	Lug. Or.	EM	2x	97.	90	20	13	17344
M		Fig. Enl. Nerv. 34 Wt.-Rap.H. Resp. Dif.2	120	120	60	60	50	146	6M	SID	8	98	100	20	43	Lug. Dr.	3M		98	93	23	12	17365
F	M	39 Nerv. Wt.-Rap.Ht.Enl.	112	170	60	90	43	123	10M	SID	5	98	100	22	74	Lug. Dr.	6M	10x	99	100	22	11	17567
F	M	30 G.I.D. Nerv.4f Wt.-Rpd.Ht. Resp.Olf2	96	205	100	100	34	66	5M	SID	6	98	100	20	45				99	80	22	14	17650
F	M	39 Rap.Ht.Resp.Dif.2 Fig.	100	120	70	50	33	107	6M	SID	3	98	80	25	19	Lug. Dr.	5M		98	100	25	7	17693
M		Fig. Nerv. Wt.- 32 Rpd.Ht. Resp.Dif. 2	120	150	80	70	43	124	6M	TID	3	90	93	25	83	Lug. Dr.	6M	2x	98	90	24	7	18431
M		37 Exoph. Nerv. Et.-	66	125	80	43	19	124	5M	SID	5	100	120		40	Lug. Dr.	3M	ply.	97	70		16	16182
F	M	38 Rt. Resp.Dif.2 Exoph. Nerv. Et.- Rpd.	110	125	80	43	30	133	6M	SID	3	98	100	20	11	Lug. Dr.			98	90	20	9	16299
M		Fig. Enl. Dis.Nerv. 37 Exoph.Rpd.Ht. Resp.Dif2	108	108	68	40	18	125	3M	TID	4	101	133	20	33	Lug. Dr.	5M	TID	98	65	20	10	16310
F	M	30 Nerv. H'dac. Enlg.	120	180	90	90	43	129	10M	SID	5	98	100	20	6	Lug. Dr.	5M	ply.	98	80	20	12	16433
M		Enl. Nerv. Wt.- 27 Rpd.Ht. Resp.Dif. 2	120	185	80	83	34	136	6M	SID	4	98	100	20	107	Lug. Dr.	6M		98	72	18	8	16438
F	M	38 Nerv. Fig. Rpd. Ht. Resp.Dif. 2	100	160	80	80	60	123	10M	SID	3	98	102	22	20				99	108	23	7	16479
F	M	40 Fig. Enl. Wt.- Nerv.Rpd.Ht. Resp.Dif2	132	124	90	34	6	118	6M	TID	6	99	116	20	20				98	84	23	15	16536
F	M	26 Dif.2 Enl. Nerv.Wt.-Rpd.Ht. Res.	108	120	68	52	12	130	5M	SID	6	98	83	20	15	Lug. Orp.	5M	SID	99	78		14	16583
M		32 Nerv.H'dac.Fig.	138	118	64	34	50	128	6M	SID	1	98	112	22	20	Lug. Drp.			99	100	23	7	16609
F	M	30 Fig. Nerv.4 H'dac.Res.Dif.2	145	150	85	65	48	112	5M	TID	8	97	88	20	47	Lug. Drp.	5M		98	75	20	17	16646
F	M	48 Appetite I Nerv.3.Rpd.Ht.Res.Dif.2	198	100	73	23	30	160	5M	TID	13	98	115	22	33	Lug. Orp.	5M		97	100	22	21	16695
F	M	32 Fig. Enl. Nerv.Wt.-Rpd.Ht.Res.Dif.	180	140	83	60	29	141	5M	SID	2	97	80	20	42	Lug. Drp.	5M		97	73	20	8	16904
F	M	40 Nerv.Wt.-Rpd.Ht.Res.Dif2	120	112	78	34	28	116	6M	SID	4	98	105	25	18	Lug. Drp.	5M		98	92	22	10	16864
F	S	33 Exoph. Nerv.Wt.-Rpd.Ht.Fig.Enl.	116	178	90	86	42	119	10M	SID	8	98	95	20	47		5M	SID	99	93	23	47	16977

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM  
INFLUENCED BY THE USE OF IODINE THERAPY

CHART 111  
Patient's Ages Ranging From 26 to 50 Years of Age.

ADMITTANCE HISTORY										IODINE AND TEST THERAPY				PRE-OPERATIVE RECORD			OP.	POST-OPERATIVE IODINE THERAPY			TIME OF DIS- CHARGE RECORD				Acc. No.
Marital	Sex	Race	Age	Chief Clinical Symptoms	Pul.	Blood Press. Syst. Dia. P-F	EMR	Wt.	Lugol's Sol'n Int. Pre. Dur.	T	P	Ret.	Wt. Spec.	Form	Ant.	Pre.	T	P	Res.	Cys. Hes.					
	F	M	42	Nerv. Rpd. Ht. Res. Dif.	120	150	90	60	36	145	5M	TID	4	98	85	20	45	Lugol	3M		98	85	20	3	16919
	F	M	49	Dif. 2. Ftg. Enl. Nerv. 3. Wtr Rpd. Ht. Res.	100	120	60	60	42	94	5M	BID	2	98	80	20	40	Lug. Drip		BID	99	82	20	7	16940
	F	M	38	Exoph. Nerv. Wtr Rpd. Ht.	90	140	100	40	35	151	5M	BID	6	98	125	25	20	Lugol	5M	Dly.	99	112	20	11	15945
	M		34	Dif. 2. Ftg. Enl. Nerv. 4. Wtr Rpd. Ht. Res.	100	150	80	70	50	141	5M	BID	3	98	100	20	140	Lugol	5M	BID	97	73	20	17	15806
	F	S	34	Dif. 2. Exoph. Ftg. Enl. Nerv. 4. Wtr Rpd. Ht. Res.	110	145	80	65	40	137	5M	BID	1	96	95	25	34	Lug. Drip	5M	Dly.	98	53	20	9	15690
	F	M	25	Exoph. Nerv. Wtr Rpd. Ht.	110	120	70	50	42	104	5M	TID	8	99	105	22	47	Lugol	5M	Dly.	92	95	20	13	15556
	M		47	Nerv. Rpd. Ht. Enl.	115	160	80	80	23	132	5M	Dly	10	97	95	22	43	Lugol	5M	Dly	99	85	20	9	15640
	M		36	Nerv. Rpd. Ht. Enl.	125	160	80	80	38	125	10M	TID	10	98	100	20	129	Lugol	5M	Dly.	94		20	15	15282
	F	M	38	Ht. Ft. Exoph. Nerv. 2. Wtr Rpd. Enl.	125	170	80	90	40	126	5M	BID	2	99	90	20	58	Lugol	5M	BID	99	90	20	6	15711
	M		37	Exoph. 2. Rpd. Ht. Hdac.	105	120			38	172	5M	BID	180				40								15554
	F	M	33	Exoph. Enl.	100	140	80	60	42	140	10M	BID	4	99	144	20	50				99	80	20	9	17228
	F	M	36	Nerv. Wtr Ftg.	100	132	74	58	56	112	5M	TID	4	99	144	20	51	Lugol	3M		99	80	22	12	17227
	M		40	Resp. Dif. Ftg. Exoph. Nerv. 4. Rpd. Ht.	104	132	68	64	50	150	5M	TID	4	98	90	25	62	Lugol	3M		97	80	20	10	16242
	F	M	47	Isorr. Ap. Nerv. 4. Wtr Rpd. Ht.	114	140	75	65	38	155	5M	BID	4	99	100	20	79	Lugol	3M		99	82	22	10	17257
	F	M	29	Ht. Res. Dif. Enl. Exoph. Nerv. 4. Wtr Rpd.	118	130	68	62	49	140	5M	BID	5	98	115	20	75	Lugol	3M		96	95	25	15	17301
	F	M	39	Enl. Nerv. 4. Wtr Rpd. Ht. Ftg.	116	130	92	38	72	98	5M	TID	3	99	95	20	51	Lugol	12M		99	95	20		16829
	F	M	41	Dif. 2. Ftg. Nerv. Wtr Rpd. Ht. Res. D	102	126	70	58	55	133	5M	BID	4	98	80	20	51	Lugol	5M	BID	98	72	18	9	16803
	F	M	39	Exoph. Nerv. 4. Wtr Ftg.	128	146	80	66	73	136	5M	BID	3	98	90	23	39	Lugol	5M	Dly	98	75	20	8	16511
	F	M	45	Res. Dif. Enl. Temp. Exoph. Nerv. 4. Rpd. Ht.	120	180	100	80	60	107	5M	BID	1	98	130	23	30	Lugol	5M	BID	98	100	22	10	17297
	F	M	38	Res. Dif. Enl. Exoph. Nerv. Wtr Rpd. Ht.	110	150	80	70	62	119	5M	BID	6		150	20	170	Lugol	5M	Dly	97	80	20	15	17384

## CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

## INFLUENCED BY THE USE OF IODINE THERAPY

CHART IV  
Patients Age Ranging From 26 to 50 Years Inclusive

ADMITTANCE HISTORY										IODINE AND BEST THERAPY			PRE-OPERATIVE RECORD			GP.	POST-OPERATIVE I & THER.		TIME OF DIS- CHARGE RECORDS.		Acc.			
Initial Sex	Initial Age	Chief Clinical Symptoms	Blood Pressure				Largel's Sol'n			T	Pul	Fec	Wt. Cpao.	Fec	Fec		Fec	Fec	Fec					
			Pol	Syst.	Diast.	P.P.	Wt.	Ant.	Pol.											Dur.				
F	M	46	Nerv.4.Wt.Res.Dif.	132	140	80	60	65	135	5M	BID	120	98	126	20	60	Larg. DTP Larg.	5M	TID	97	78	22	11	17419
F	M	41	Nerv.4.Wt.Rpd.Ht.Enl.	132	150	80	70	60	122	5M	TID	5	98	80	20	55	Larg.	5M	Dly	98	80	22	12	16624
F	M	28	Exoph.Nerv.Wt.Res.Dif.1	120	135	70	65	75	136	5M	TID	1	98	105	22	41	Larg.	1M		98	72	20	10	17449
F	M	39	Dif.GID. Exoph.Nerv.4.Rpd.Ht.Res.	122	135	70	65	75	147	5M	TID	6	97	105	22	79	Larg. DTP Larg.	1M	TID	98	90	20	13	17524
F	M	25	Nerv.Rpd.Ht.Res.Dif.2.Ftg.	126	150	84	66	75	125	5M	TID	15	99	100	22	90	Larg. DTP Larg.	1M		95	72	20	21	17523
M		41	Nerv.4.Exoph.4.Enl.	126	180	70	60	66	185	10M	BID	4	97	95	20	108	Larg. DTP Larg.			97	80	22	10	17570
M		42	Enl. Exoph.Nerv.Res.Dif.Ftg.	132	164	140	24	56	168	10M	TID	5	97	125	22	123	Larg. DTP Larg.	5M	Dly	98	120	20	13	17569
F	M	34	Enl.Rpd.Ht. Exoph.Nerv.Res.Dif.2.Ftg.	120	144	82	62	75	134	5M	BID	5	98	120	25	123	Larg. DTP Larg.	1M	BID	99	85	20	11	17729
F	M	35	Ftg.Enl. Nerv.4.Wt.Rpd.Ht.Res.Dif.	96	140	90	60	61	118	5M	TID	1	98	72	20	35	Larg. DTP Larg.	1M	BID	99	75	20	5	17725
F	M	45	GID. Nerv.Wt.Rpd.Ht.Res.Dif.2	120	100	80	20	60	104	5M	BID	3	96	72	20	55	Larg.	1M	BID	97	86	20	9	17815
M		36	Nerv.Wt.Ftg.Nocturia Exop	96	140	70	70	54	111	10M	TID	1	98	75	22	64	Larg.	1M	BID	97	58	20	9	17816
M		40	Ftg. Exoph.Nerv.3.Wt.Res.Dif.1	108	134	78	56	55	100	5M	TID	2	99	105	25	40	Larg. DTP Larg.	1M	BID	96	100	20	9	18199
F	M	38	Ftg.Enl.GID Nerv.Wt.Rpd.Ht.Res.Dif.2	110	200	80	120	73	124	5M	TID	3	98	110	22	45	Larg. DTP Larg.			98	80	20	8	18223
M		47	Exoph.Nerv.Wt.Rpd.Ht.Enl.	115	150	90	60	54	188	5M	BID	6	98	95	20	48	Larg. DTP Larg.			99	90	20	9	18748
M		35	Nerv.4.Wt.Res.Dif.2.Ftg.	100	135	85	70	62	120	5M	TID	5	99	85	18	60	Larg. DTP Larg.			99	80	20	12	18744
F	M	42	Exoph.Nerv.Wt.Rpd.Ht.Enl.	125	140	80	60	54	107	10M	BID	4	98	120	22	12	Larg. DTP Larg.	1M	BID	97	85	20	11	18745
M		38	Nerv.Wt.Rpd.Ht.Ftg.	120	151	100	61	99	118	10M	BID	7	98	112	20	65	Larg. DTP Larg.			99	98	22	13	18782
F	M	39	Exoph.Nerv.4.Ftg.Enl.GID	130	136	76	60	55	102	10M	TID	13	98	85	22		Larg. DTP Larg.	1M	BID	98	85	20	17	18833
M		39	Nerv.Wt.GIDb.Rpd.Ht.Enl.	120	150	90	60	80	150	10M	TID	12	99	80	22	115	Larg. DTP Larg.	1M	BID	99	92	20	17	18833
F	M	31	Dif.Enl. Exoph.Nerv.4.Rpd.Ht.Res.	130	160	90	90	55	105	5M	BID	6	99	92	20	70	Larg. DTP Larg.	1M	BID	98	74	20	14	18799



## CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

## INFLUENCED BY THE USE OF IODINE THERAPY

## CHART V

Patients Ages Ranging From 25 to 50 Years Inclusive

ADMITTANCE HISTORY										IODINE AND TEST THERAPY		PRE-OPERATIVE RECORD		POST-OPERATIVE TYPE I THERAPY		TIME OF DIS- CHARGE REC.		Acc. Co.			
Marital Sta	Age	Chief Clinical Symptoms	Blood Press.				Iodine Sol.				Ft. Spec	Pul. Res.		T. Pre.		T. Post.					
			Pul	Syst	Diast	P.P.	HR	Wt.	Ant.	Pul	Dur.	T.	Pul	Res.	Gr.	Pre	Post	Days			
M	40	Exoph. Nerv. 4. Wt. Rpd. Rt. Res. Dif. 1.	120	135	80	85	54	144	5M	TID	2	98	85	20	41	Log. Dip.	98	72	20	22	14658
F M	40	Exoph. Nerv. Wt. Rpd. Rt. Enl.	135	180	100	80	50	124	5M	BID	4	98	85	22	63	Log. Dip.	98	80	20	12	15314
F S	26	Wt. Res. Dif. 1. Enl.	110	115	68	47	30	104	15M	Dly	16	93	100	20	30	Log. Dip.	98	96	20	21	15312
F M	47	Nerv. Rpd. Rt. Res. Dif. 2	96	124	84	40	42		10M	TID	3	98	106	22	0		99	95	20	14	13850
F S	32	Wt. Enl. Nerv. Rpd. Rt. Res. Dif. 2. CID. Wt.	120	120	80	40	40	121	10M	TID	9	98	90	20	57	Log. Dip.	100	85	22	19	13699
M	39	Exoph. 4. Nerv. 4. Wt.	120	160	100	60	40	117	10M	TID	3	98	120	20	55	Log. Dip.	98	80	25	8	13789
M	45	Nerv. 3. Wt. Rpd. Rt. Res. Dif. 2. Enl.	110	165	90	75	28	127	10M	TID	2	98	100	20	47	Log. Dip.	100	85	20	7	14512
F S	38	Enl. Exoph. Nerv. 3. Rpd. Rt. Res. Dif.	100	130	80	50	30	118	10M	TID	10	98	95	22	139	Log. Dip.	100	88	22	10	13753
F M	35	Nerv. Wt. Res. Dif. 1. Freq. Mictur.	05				20		10M	TID	4	98	75	20	25	Log. Dip.	98	75	25	9	13900
F M	31	Dif. 2. Enl. CID Exoph. Nerv. 4. Rpd. Rt. Wt. Res.	120	170	80	90	30	129	6M	TID	5	99	80	25			99	92	22	14	13982
M	32	Nerv. Wt. Rpd. Rt.	120	135	60	75	58	178	10M	TID	2	99	100	22	17	Log. Dip.	100	90	20	8	14437
F M	29	Nerv. 4. Wt. Rpd. Rt. Res. Dif. Enl.	110	110	90	25	45	144	10M	TID	7	98	85	20	112	Log. Dip.	100	95	20	12	14316
M	40	Wt. Sleepy. Cold hands.	80				8	186	10M	TID	1	97	73	20	62		98	75	20	5	14286
F M	36	Nerv. Incom. Excess. App.	140	160	85	64	20	135	10M	TID	21	99	132	20		Log. Dip.	98	95	20	150	14318
M	36	Rpd. Rt. Res. Dif. 2. Wt.	92	145	80	65	38	136	5M	TID	6	97	95	20	16		97	72	20	11	14024
F M	37	Exoph. Nerv. Rpd. Rt. Enl.	130	165	70	95	40	122	10M	TID	5	98	95	20	54	Log. Dip.	98	100	20		14059
F M	40	Wt. Rpd. Rt. Wt.	150			32		10M	TID	5	98	115	22	42	Log. Dip.	98	80	20	12	14888	
M	46	Dif. Enl. Exoph. Nerv. 3. Wt. Rpd. Rt. Res.	120	135	70	85	44	137	10M	TID	5	99	110	22	102	Log. Dip.	98	100	20	13	14534
F M	35	Dif. 2. Enl. Exoph. Nerv. 4. Wt. Rpd. Rt. Res.	100	140	70	70	32	95	10M	TID	3	99	115	20	86	Log. Dip.	98	75	20	10	14600
F M	29	Wt. Nerv. 4. Rpd. Rt. Res. Dif. 2. Enl.	100	135	70	65	34	134	10M	TID	5	99	125	22	40	Log. Dip.	100	80	22	15	14932

## CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

## INFLUENCED BY THE USE OF IODINE THERAPY

CHART VI  
Patients Ages Ranging From 26 to 50 Years Inclusive

ADMITTANCE HISTORY										IODINE AND POST-OPERATIVE RECORD				PRE-OPERATIVE RECORD				POST-OPERATIVE IVE 1 TEST				TIME OF DISCHARGE				Ass.
Marital	Sex	Age	Chief Clinical Symptoms	Blood Press.				Wt.	Hemoglobin			T. Pul. Res.			Gr.	T. Pul. Res.			T. Pul. Res.			T. Pul. Res.				
Mar.	Sex	Age		Pold	Sys	Dia	P.F.	Wt.	Ant.	Post.	T.	Pul.	Res.	Gr.	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th		
F	S	26	Ht. Enl. Nerv. 4. Wt. Res. Dif. 2. Rpd.	120	130	75	55	52	95	102	112	2	99	105	22	50	149	102	112	99	68	20	7	14931		
F	M	40	GID. Enl. Nerv. 4. Rpd. Ht. Res. Dif. 2.	130	118	80	78	45	142	102	112	6	99	100	20	29	149	52	112	99	62	20	12	15070		
F	M	26	Nerv. 3. Wt. Rpd. Ht. Res. Dif.	125	130	75	50	31	95	112	112	3	99	125	20	25	149	52	112	99	60	20	12	15065		
F	M	30	Exoph. Nerv. 4. Wt. Rpd. Ht. Enl.	138	120	70	42	45	108	102	112	2	97	95	20	42	149	52	112	99	100	20	7	15060		
F	M	32	Hoarseness Exoph. Nerv. 3. Wt. Rpd. Ht. Enl.	100	150	80	70	29	124	102	112	2	98	60	18	181	149	52	112	99	62	20	13	15121		
F	M	39	Nerv. Wt. Rpd. Ht. Enl. GID.	80	120	60	50	30	102	102	112	3	97	60	22	35	149	52	112	97	72	20	13	15155		
F	M	33	Nerv. 4. Wt. Res. Dif. 2.	100	140	50	90	37	95	112	112	3	98	100	22	40	149	52	112	98	106	20	8	16269		
F	M	20	Nerv. Stg.	175				32	133	95	112	8	92	100	20	49	149	52	112	98	95	20	15	16770		
F	M	35	Ftg. Ht. Enl. Ftg. Exoph. Nerv. 3. Wt. Res. Dif. 2.	120	130	90	40	27	124	95	112	10	98	125	20	61	149	52	112	99	60	20	16	16909		
F	M	32	Nerv. Ftg. Rpd. Ht. Enl.	120	130	80	50	40	95	95	112	3	90	115	25	74	149	52	112	97	78	20	9	17011		
F	M	36	Nerv. 1. Rpd. Ht. Ftg. Enl. GID.	130	140	60	60	73	120	95	112	3	98	99	25	39	149	52	112	99	92	20	8	16269		
F	M	28	Ftg. Enl. GID Exoph. Nerv. 4. Wt. Rpd. Ht.	120	175	80	56	60	117	95	112	5	99	120	22	110	149	52	112	99	90	20	8	16289		
F	S	30	Nerv. Wt. Rpd. Ht. Enl.	120	168	68	100	60	99	95	112	11	98	115	20	69	149	52	112	99	72	20	21	16091		
F	M	46	Dif. Ftg. GID. Exoph. Nerv. Wt. Rpd. Ht. Res.	100	210	100	110	61	158	95	112	2	99	85	22	59	149	52	112	99	60	22	9	16513		
F	M	35	GID. Nerv. Wt. Rpd. Ht. Res. Dif.	110	140	80	60	60	116	95	112	5	98	90	22	41	149	52	112	97	72	20	11	16663		
F	M	41	Rpd. Ht. Exoph. Nerv. 4. Wt. Res. Dif.	120	160	80	80	51	132	95	112	3	99	85	25	55	149	52	112	98	75	20	11	16723		
F	M	39	Nerv. 4. Wt. Rpd. Ht. Ftg. Enl.	116	130	92	38	72	98	95	112	3	99	95	20	60	149	52	112	99	95	20	14	16829		
F	M	34	Ftg. Enl. Exoph. 1. Nerv. 4. Res. Dif.	110	165	80	85	56	160	95	112	3	98	100	20	69	149	52	112	99	78	20	8	16921		
M		33	Enl. Nerv. 4. Wt. Res. Dif. 2. Ftg.	100	130	70	60	60	114	95	112	9	99	100	20	68	149	52	112	98	100	20	16	16994		
F	M	33	Nerv. Wt. Rpd. Ht. Res. Dif.	120	140	70	70	74	141	95	112	3	97	95	20	49	149	52	112	97	72	20	8	17016		

## KEY:-

CHIEF CLINICAL SYMPTOMS:- Exoph.-Exophthalmos, Nerv.- Nervousness, Ht.- Loss of Weight, Rpd. Ht.- Rapid Heart, Res. Dif.- Respiratory Difficulty, 1, 2, or 3 - Degree of Res. Dif., Ankles.-Idema of Ankles, G.I.D.- Gastro-Intestinal Disorders, Enl.- Enlarged Thyroid, Wt.- Muscular Weakness.

tigue, exhaustion, weakness, loss of weight, nervousness, rapid heart, respiratory difficulties were present in all of the cases and in a number (15) variation in appetite, nausea, vomiting and diarrhea.

Exophthalmos was observed five times in each of groups 1 and 3 and 36 times in group 2, a total of 46 or

35%. The greatest number of such manifestations was in the third decade.

Certain circulatory disturbances always noted in hyperthyroidism were present. The average pulse rate was 118, 115 and 109 in groups one, two and three respectively. While there is no marked difference in these rates there is some evidence that there is a

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM  
INFLUENCED BY THE USE OF IODINE THERAPY

CHART VII  
Patients Ages Ranging Above 50 Years

ADMITTANCE HISTORY										IODINE AND REST THERAPY		PRE-OPERATIVE RECORD			OP.	POST-OPERATIVE THERAPY			TIME OF DIS- CHARGE				Acc. No.
Marital Status	Age	Chief Clinical Symptoms	P	Syst	Diast	P.P.	Wt.	Am.	Pre	Post	T	P	H	Wt. Spec in Gm.	Pre- Op.	Post- Op.	Pre- Op.	T	P	R	Hos		
M	55	Dif. G.I.D. Exoph. Nerv. Wt. Rpd. Ht. Res.	90	140	80	60	40	118	10M	TID	13	98	100	22	95	Lug- Dr.	10M	0	95	100	22	19	26103
F	58	Exoph. Nerv. 4. Wt. Rpd. Ht.	100	150	100	80	30	107	10M	TID	3	99	100	20	31	Lug- Dr.	10M	TID	98	85	20	9	15049
F	57	Exoph. Nerv.	120	216	100	116	45	116	2M	BID	100	98	95	20	30	0	0	0	100	108		16363	
M	69	Nerv. Wt. Rpd. Ht. Res. Dif.	100	160	85	56	12	123	15M	Dly	175	98	90	22	40	Lug- Dr.	0	0	98	80	20	182	17019
F	64	Nerv. Wt. Rpd. Ht. Wcn.	138	160	78	82	40	147	5M	TID	9	98	100	20	64	Lug- Dr.	5M	TID	98	85	20	22	16540
F	58	Nerv. Rpd. Ht. Res. Dif. CID.	120	107	74	35	40	107	5M	TID	3	98	100	20	32	Lug- Dr.	5M	BID	98	80	20	10	16807
M	53	Nerv. Rpd. Ht. Wcn. Enl.	120	130	85	45	30	125	5M	BID	3	98	105	20	52	Lug- Dr.	5M	Dly	98	100	20	10	15930
M	59	GID. Enl. Ankles Nerv. 3. Wt. Rpd. Ht. Res. Dif.	110	130	60	70	50	106	5M	BID	8	98	105	25	32	Lug- Dr.	5M	Dly	97	100	20	12	15938
M	52	Nerv. Wt. Rpd. Ht. Res. Dif. Wcn.	80	140	65	75	35	171	5M	TID	3	98	95	25	85	Lug- Dr.	5M	BID	98	90	24	7	15431
F	64	Nerv. 4. Wt. Rpd. Ht. Enl.	115	150	80	70	55	80	5M	BID	5	100	130	25	60	Lug- Dr.			98	80	22	15	15053
M	52	Wt. Rpd. Ht. Wcn. Enl.	120	170	70	100	94		10M	TID	4	98	100	24	123	Lug- Dr.	10M	TID	99	85	25	11	14858
M	55	Nerv. Rpd. Ht. CID.	100	190	70	110	30	137	10M	TID	7	97	70	20	42	Lug- Dr.	10M	TID	98	72	20	12	13863
M	52	Exoph. 4. Nerv. 3. Wt. Rpd. Ht.	100	150	60	90	40	135	10M	TID	4	99	72	20	105				99	96	20	10	14329
M	54	Res. Dif. Enl. Exoph. Nerv. 3. Wt. Rpd. Ht.	110	200	90	110	38	155	10M	BID	4	97	90	22	45				98	95	20	11	14430

## KEY.

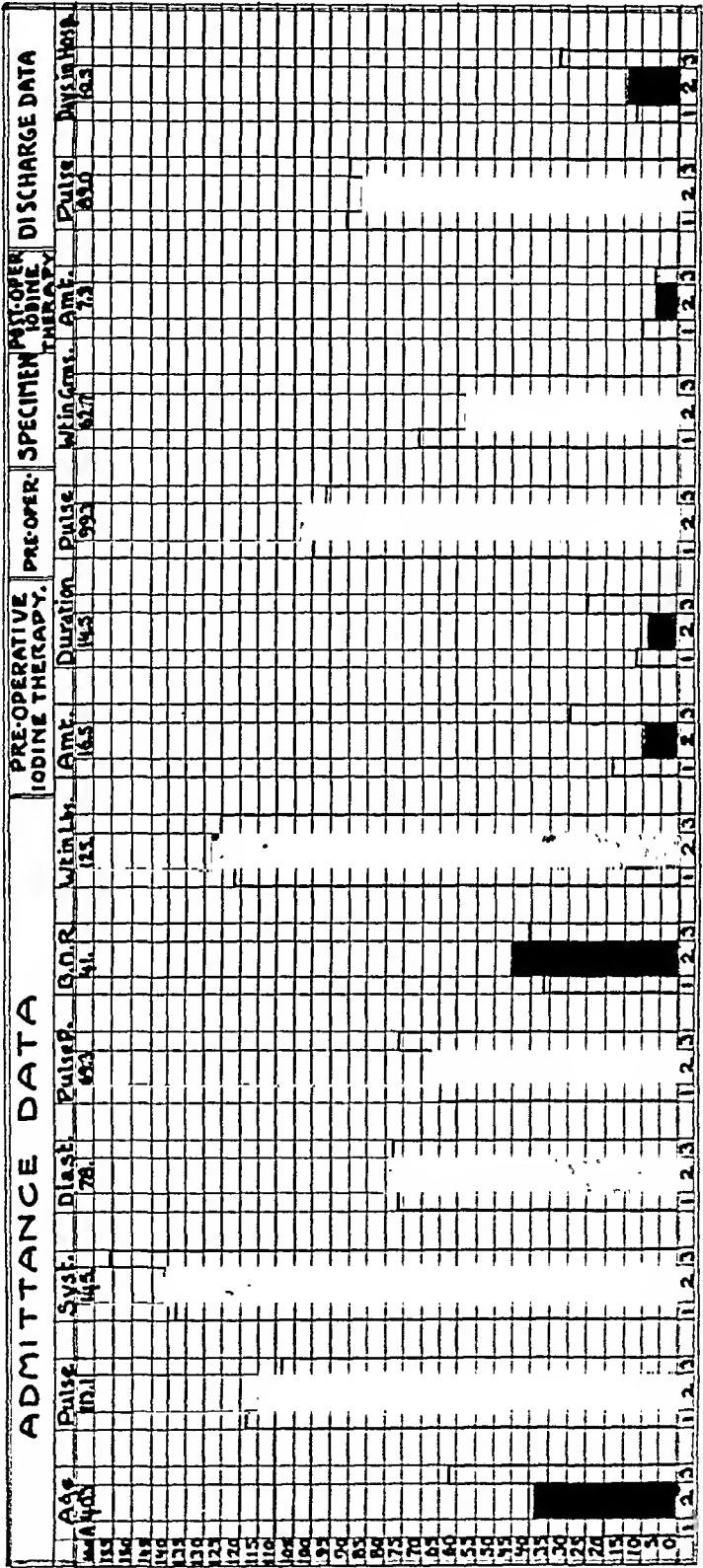
CHIEF CLINICAL SYMPTOMS:- Exoph.- Exophthalmos, Nerv.- Nervousness, Wt.- Loss of Weight, Rpd.Ht.- Rapid Heart, Res.Dif.- Respiratory Difficulty, 1,2,or3 -Degree of Res.Dif., Ankles- Edema of Ankles, G.I.D.- Gastro-intestinal Disorders, Enl.-Enlarged Thyroid, Wcn.-Muscular Weakness.

progressive decrease in pulse rate according to increasing age. The average systolic blood pressure was 138, 141, 156 and the diastolic pressures: 72, 79, 87 in the respective groups. There is also evidence here of an increased vascular tension which is independent of the usual structural changes in the vessel walls, although the increase with the age is indicative of factors other than toxicity from thyroid overfunction. For the same reason the pulse pressure was observed to be greater in the older individuals, although the general average was high (69.3). The average positive basal

metabolic rates were as follows: 37.1, 45.4, 41.4. The lowest was 8 and the highest 94. Occasional high rates were observed in the extremes of the ages, but in general they were higher in the third decade. Pregnancy, with its great metabolic demands, is probably a great factor during this period. The basal metabolic readings were the averages of several different readings at different times. There was general evidence in loss of weight, which in many instances occurred rapidly. The average weight was 125 pounds with very little difference in the averages of the respective groups. (See chart 8).

SCHEMATIC COMPARISON OF DATA BASED UPON  
THE AVERAGES IN THE 3 GROUPS

CHART No. 8



Preoperative treatment consisted of rest in bed and iodine therapy. The latter was always given in the form of Lugol's solution in water two or three times a day in 5 or 10 minim doses according to the judgment of one of us (Joyce) as to the toxicity of the individual patient. This is in accord with the guiding principle ordinarily carried out at the Mayo Clinic. The average amount of Lugol's solution given was 16.5 c.c. during an average duration of 14 days. Both of these averages are augmented by the inclusion of a few cases in which iodine was administered over a long period of time (180 days). When such instances are excluded the average dose becomes 7.1 c.c. and the average duration 5.9 days, although the time of treatment in several patients was only for one day. Following this preoperative treatment there occurred, as a rule, an arrestment of subjective symptoms and concomitant with such a change a decrease in the pulse rate by an average of 13.8 per minute. In some individuals (17) there was an actual increase in the pulse rate, or in others (15) it remained constant following the use of iodine. Operative procedure was instituted after a definite break in the severity of the symptoms and an established lowered pulse rate.

Double lobectomy was the surgical procedure followed. The amount of gland removed was based upon the degree of enlargement and the clinical data obtained both before and after the use of iodine. When such specimens were weighed in the fresh state it was found that the average weight in the three groups was 70.8 gm., 57.4 gm. and 59.7 gm. These weights al-

though they represent only a portion of the gland are above the average weight (40 gms.) of the entire adult gland. The glands of group 1 were as a rule somewhat larger. In those patients who received iodine over a considerable period of time the gland tissue was more abundant and the increased weight appeared to be connected with the colloid increase. The policy of one of us (Joyce) has been to remove as much gland tissue as possible, avoiding injury to the recurrent laryngeal nerve or encroaching upon the region of the parathyroids.

The administration of iodine after the operation in some of the patients consisted in giving Lugol's solution (Lugol's 100 minims in 2% of Sod. bicarbonate and 5% glucose) by the Murphy drip method, and also Lugol's by mouth. The average amount given after operation was 7.3 c.c. In 15 instances none was given. In 34 cases one administration by the Murphy drip method referred to above sufficed. In all of the others small doses of Lugol's were given in addition to this.

It is interesting to note the length of time that these patients remained in the hospital with this combined method of therapy. We did not consider it practical or advisable to subject the patients to the determination of the basal metabolic rate during the post-operative period but we have relied upon the cessation of clinical symptoms and the constancy of a lowered pulse rate. Discharge of the patient from the hospital was considered as safe when the pulse rate remained below 100 under varying conditions and the healing of the wound was uneventful. In this series the average

period of hospitalization was 19.3 days. This average was 11.6 days after correction because of other complication in a few of the cases.

Pathological examination of the portions of the glands removed, revealed all of them to be free from nodules with the exception of three, in which there were small solitary foetal adenomata of no consequence. The glands were, in general, variable in consistency and color. In only a few instances was there the usual ischemic, fleshy, colloid free type of gland so commonly observed in hyperthyroidism prior to the present regimen which is being followed by the preoperative use of iodine.

The capsule and supportive stroma was generally increased in those glands coming from older individuals. However, in some of the specimens from the younger patients marked diffuse fibrosis was noted. The basis for such an increase probably lies in the irritation hyperplasia of connective tissue associated with cyclic functional hyperactivities and recessions, and is probably proportionate to the degree of such changes. In older individuals there is added to this the influence of circulatory deficiency because of arteriosclerosis. Except in a few instances colloid was always visible. In some cases (those given iodine over a long period of time) it was abundant. A general increased translucency of thin sections was observed. The surfaces made by sectioning were generally pinkish red and diffusely mottled with greyish specks or small poorly defined blotches. In none of these glands was there gross evidence of cystic degeneration. Vascularity was less prom-

inent than in the glands in which iodine was not used. All in all the gross appearance of the thyroid, after iodine administration as compared to those removed without its pre-operative use, is similar to the lung in broncho-pneumonia when compared with that of lobar pneumonia in the stage of gray hepatization.

With the above clinical facts and gross pathology in mind, a detailed study of the histologic changes in the different glands of the three groups was made. The selection of blocks from different parts of the gland was determined by gross variations seen by making many different gross sections of the specimen. Microscopic sections were stained with hematoxylin and eosin with the exception of a number of frozen sections which were stained with Sudan III.

Observations were made concerning the size of the acini, their colloid content, the degree and character of epithelial change, as well as the variations in the supportive stroma and its vascular channels (see chart IX). The size of the acini varied in these instances, as it always does in direct ratio to the colloid content, and at tent. The latter varied from complete absence to large coalescent masses. Such accumulations were found in 52% of group 1, 26% of group 2, and 21% of group 3. In all of these instances iodine had been given over a considerable period.

Hyperplasia and hypertrophy were in general spotty and varied in indirect ratio to the colloid content, and at times it was as marked as is seen in the glands of patients to whom iodine had not been given. In these latter

## CHART IX CONCERNING LIPOID BODIES

In Selected Specimens From

The Three Groups

## LIPOID BODIES

Clinical Data				EPITHELIUM													COLLOID		STROMA	
Acc.	Age	Iodine		Acinar					Intra-acinar				Inter-acinar				Lip.	Spher.	Rest Lip.	
No.	Yrs.	amt.	Dur.	Type	No. bodies	Size	Loc.	Spheroid	No. cells	No. bodies	Size	Loc.	No.	Size	Loc.	Body	Body	Fet	Body	
17265	2D	3.	5	L.cu.	9	X	Diff.	1 occas.	—	—	—	—	4	X	Diff.	—	1	—	—	
14211	15	13.	13	L.cu.	6	X	Diff.	—	25	S	X	Diff.	6	X	Diff.	—	—	—	—	
14661	17	1.5	4	L.col.	7	X	l.p.	1 occas.	1	S	X	Diff.	4	X	Diff.	—	1	—	—	
14518	19	2.D	2	L.col.	11	X	Diff.	l.p.	—	6	S	X	Diff.	1D	X	Diff.	—	1	—	+
17728	22	1.D	1	Col.	19	X	l.p.	—	8	S	X	Diff.	13	X	Diff.	—	1	—	+	
13624	22	12.0	6	L.col.	21	X	Diff.	1 occas.	6	S	X	Diff.	8	X	Diff.	—	1	—	—	
16535	25	2.D	3	L.col.	9	Y	Diff.	1-2	2	S	Y	Diff.	5	Y	Diff.	—	2	+	—	
147D5	22	72.D	120.	L.cu.	3	X	Diff.	—	—	—	—	—	2	X	Diff.	—	—	—	—	
15312	26	48.D	16	Cu.	22	Y	Diff.	—	6	S	Y	Diff.	14	Y	Diff.	+	1	—	—	
14316	29	14.D	7	L.col.	13	Y	Diff.	1 occas.	2	S	Y	Diff.	7	Y	Diff.	—	2	—	—	
16458	27	2.75	4	L.cu.	9	X	Diff.	—	—	—	—	—	4	X	Diff.	—	—	—	+	
16666	30	8.D	8	Cu.	9	Z	Diff.	—	2	S	Y	Diff.	6	Y	Diff.	—	1	+	—	
17635	34	8.D	8	Cu.	7	Z	Diff.	—	1	S	Y	Diff.	6	Y	Diff.	—	1	+	—	
14744	35	5.0	5	Cu.	11	Y	Diff.	—	—	—	—	—	7	Y	Diff.	—	—	—	—	
10479	38	3.25	5	L.cu.	8	Y	Diff.	—	2	S	Y	Diff.	5	Y	Diff.	—	1	—	—	
16536	40	6.0	6	Cu.	5	X	Diff.	1-2	1	S	Z	Diff.	4	Z	Diff.	—	2.8	—	—	
17569	42	10.0	5	L.cu.	5	Z	Diff.	1	1	S	Z	Diff.	3	Z	Diff.	—	1	—	—	
15440	47	3.25	10	L.cu.	0-5	Y	Diff.	1	1	S	Y&Z	Diff.	4.0	Y&Z	Diff.	—	1	+	—	
16199	48	2.0	2	L.cu.	4	Y&Z	Diff.	—	—	—	—	—	3	Y&Z	Diff.	—	1	+	—	
1595D	53	2.0	3	Cu.	7	Y	Diff.	—	1	S	Y	Diff.	0-4	Y	Diff.	—	1	—	—	
14858	52	8.0	4	L.cu.	4	Z	Diff.	—	5	S	Z	Diff.	0-3	Y	Diff.	—	1	+	—	
15938	59	5.3	8	Cu.	6	Z	Diff.	—	4	S	Z	Diff.	2	Z	Diff.	—	1	—	—	
13863	55	14.0	7	Col.	4	Z	l.p.	—	1	S	Z	Diff.	4	Z	Diff.	—	1	—	—	
17019	69	175.0	175	Cu.	9	Y	Diff.	—	1	S	Y	Diff.	3	Y	Diff.	—	1	+	—	
16363	67	66.0	1D0	Cu.	5	Y&Y	Diff.	—	—	—	—	—	4	Y&Y	Diff.	—	1	—	—	
1694D	64	9.0	9	L.cu.	7	Y&Y	Diff.	—	—	—	—	—	7	Y&Y	Diff.	—	—	—	—	

Key to abbreviations:— (I) Type of Epithelium: L.cu.—Low cuboidal; Cu.—Cuboidal; Col.—Columnar; L.col.—Low columnar;  
 (II) Size of Lipoid Bodies: X—Small and fine; Y—Medium; Z—Large and coarse;  
 (III) Location and Distribution of Lipoid Bodies: Diff.—Diffuse; L.P.—At Inner Pole;  
 S.—Solidly filled.

cases iodine in small doses had been given for a day. Fewer intra-acinar papillary projections were seen in group 1. In most of the glands studied, evidences of progressive stretching with blunting of the intra-acinar papillary projections was observed. In many cases they were entirely erased. Many acini were lined by band-like accumulations of slightly hyperplastic epithelium. The inter-acinar epithelium showed changes that varied in a

manner similar to that lining the acini. In some of the instances (those given iodine for a long time) there was evidence of a marked hyperplasia and hypertrophy of the inter-acinar epithelium with the formation of numerous newly formed small acini. Such changes were generally observed in glands having either focal or general excess accumulations of colloid. (See photomicrograph No. 1). The greatest variation in epithelium was observ-

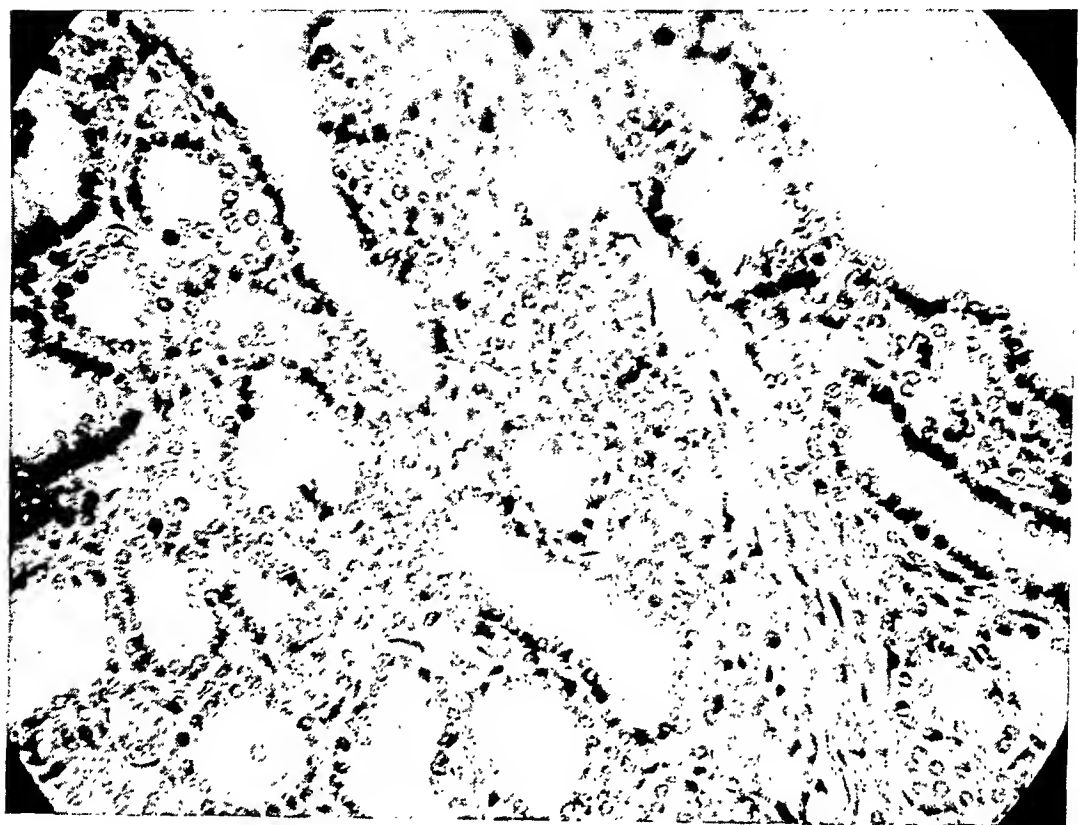


FIG. 1

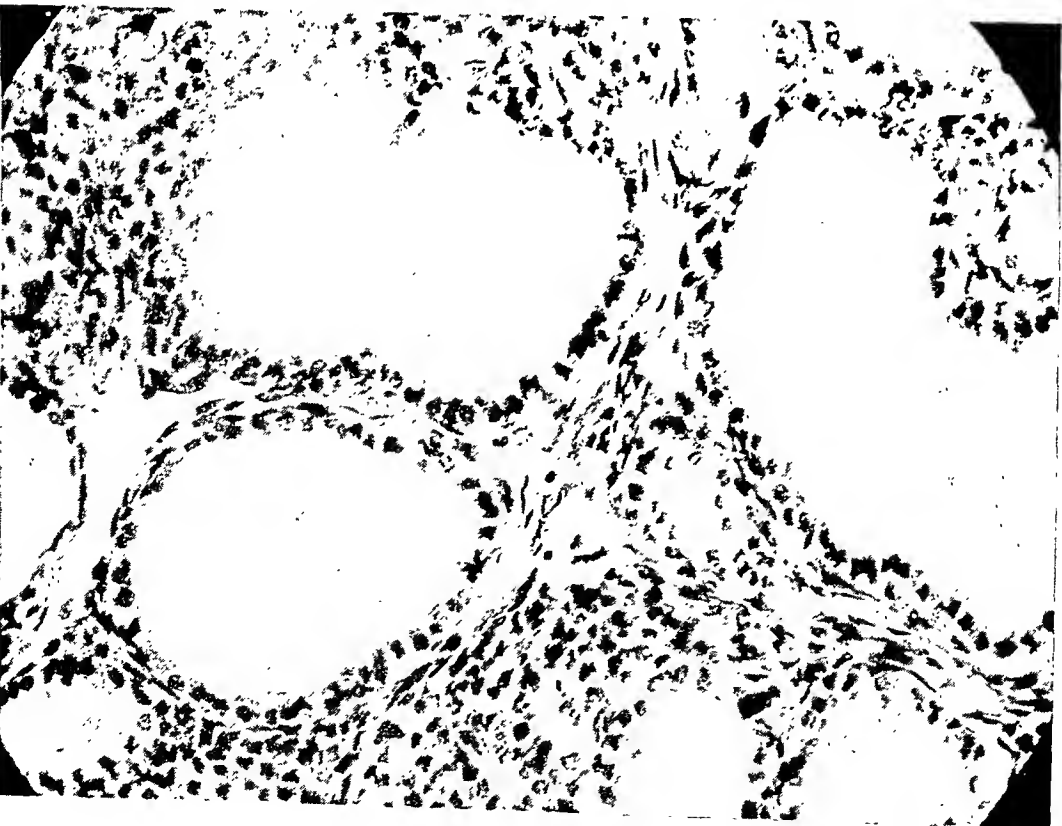


FIG. 2



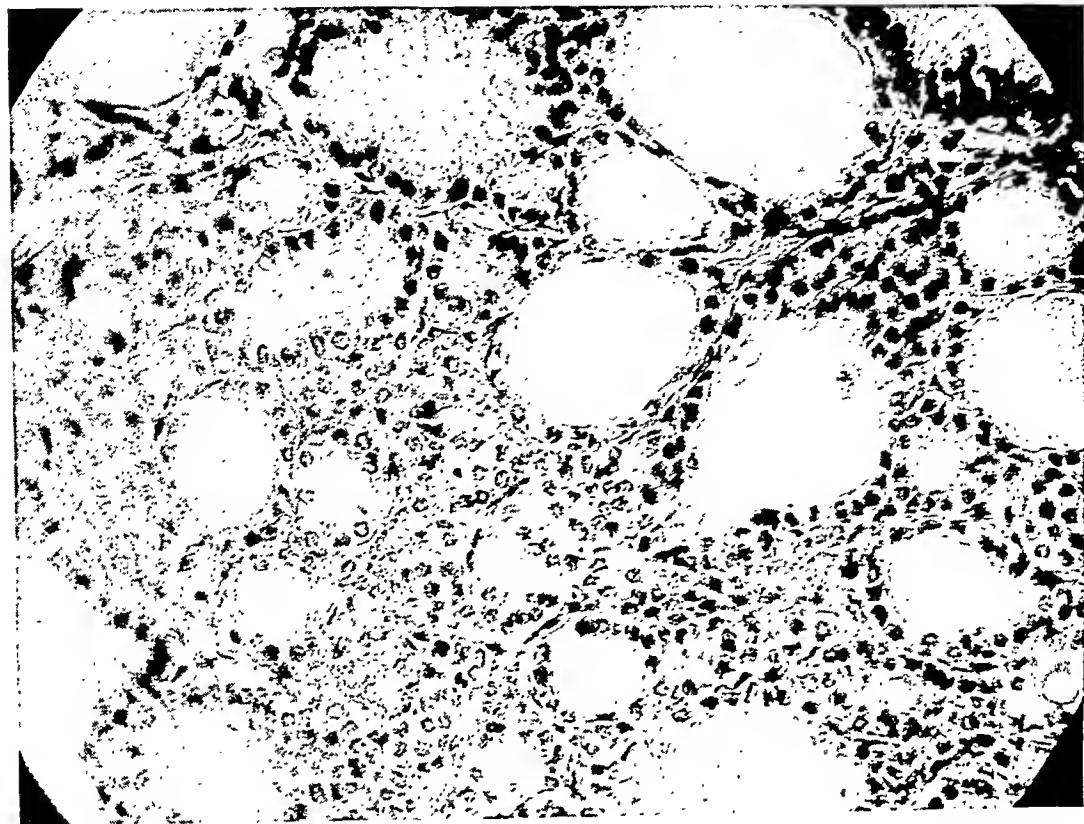


FIG. 3

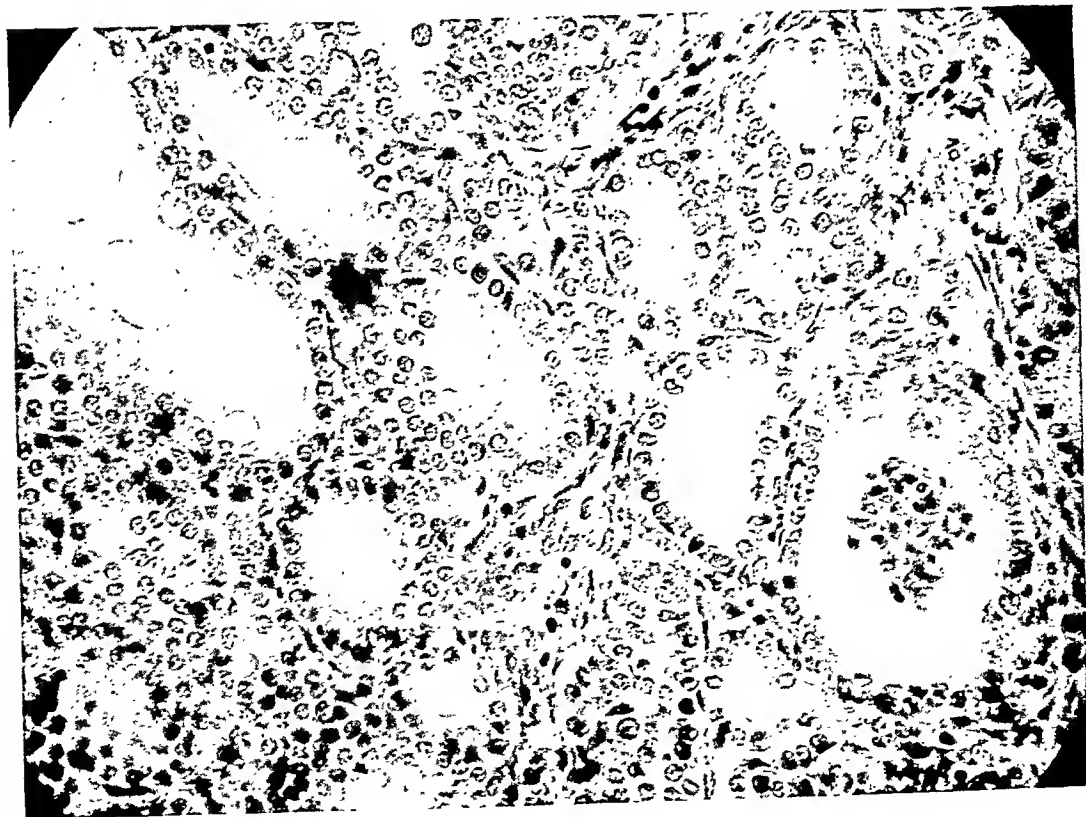


FIG. 4

ed in groups 2 and 3. A patchy stroma variation was also seen. In the glands of younger individuals fibrosis was always found at the sites of greatest hyperplasia, but it was generalized in only a few instances. A gradual reduction in the supportive stroma content was found as the inactive areas were approached. In the glands of older individuals, a definite perivascular fibrosis with marked hyaline changes was often seen. Such scarred areas were frequently observed to be fringed with numerous small acini.

They generally appeared broadest about the borders of such hyperplastic areas and narrowest as they passed through regions with colloid bulging acini.

The blood vessels showed less general and considerably less focal engorgement than is commonly seen in untreated glands. Endarteritis was observed eight times (8%) in group 2 and nine times (64%) in group 3. No such changes were seen in group 1.

On the basis of such histologic studies the degree of involution was

GRADING OF ABNORMALITY IN SPECIMENS OF INSTANCES  
OF HYPERTHYROIDISM ON THE BASIS OF THE  
DEGREE OF INVOLUTION  
CHART X

Age Limits	No. of Cases	Groups	Grade I	Grade II	Grade III	Grade IV
0 - 25	17	1	6	6	5	0
26 - 50	100	2	32	45	23	0
51 +	14	3	3	8	3	0
Total	131		41	59	31	0

So-called round cell infiltration was not found to be extensive. This too was found to be spotty in its distribution. It was much less frequent in group 1 than in groups 2 and 3. These lymph cells did not seem to vary from their usual character or distribution. Pseudo-lymph nodes were found two times in group 1, 30 times in group 2, and not at all in group 3.

The estimation of the degree of lymph vessel dilatation is somewhat more difficult. Sometimes these channels were widest in the areas of increased activity, and other times they appeared to be actually obliterated by the pressure of cells on their walls.

estimated and the specimens were graded, as to the extent of the abnormality that was evident (see chart X). In grade 1 there was sufficient involution so that the nearest approach to normal was observed, while in grade 4 the conditions would be similar to those seen in untreated glands. (See microphotographs 2, 3, 4). All of the 131 examined had undergone some degree of involution. One hundred (76%) of all of these showed at least 50% reversion on the basis of histologic changes. While this study was in progress Sager (vide supra) published a similar method of grading the pathological changes.

Recently Jaffe (15) has brought to  
(15) *Arch. Path. & Lab. Med.*, 3:955-962  
(June) 1927.

our attention certain histologic studies concerning the lipoid bodies of the thyroid. He observed a gradual increase in number and size of such granules up to puberty, and pointed out that its influence later in life had not been established. Varying notions of the significance of such lipoid content have been advanced, namely (1) that it may be related to cell waste products, (2) that it originates from desquamation of epithelium and (3) that it is an actual secretory substance. Jaffe concluded that the excretion of lipins starts after the first year of life and increases with age. Also that they are products of secretory activity of the epithelium and are discharged into the colloid where they are dissolved. In addition he found a Sudan III staining substance in the plasma.

It seemed of interest to study the results obtained by stained sections (Sudan III) from selected instances (26) with ages ranging from 15 to 69 years, under the influence of varying amounts of iodine (see chart XI). The lipin content of the epithelium, colloid and stromas was noted.

The number of lipin granules in the acinar epithelium varied from 5 to 22 in the different instances. They were most numerous in the glands of individuals below the age of 35. The granules were largest in the glands of older individuals. They were diffusely scattered through the cells. Spheroid bodies were only occasionally found in the colloid. A much smaller number of lipin granules were found in the

desquamated intra-acinar epithelium. They were generally larger but similarly distributed. The granules in the inter-acinar epithelium were generally somewhat larger and varied from 2 to 14 in number. No lipins were seen in the colloid. A small number of spheroid bodies were seen here. Most of the interacinar blood vessels contained sudanophil plasma. No sudanophilic substance was seen in the lymphatics.

The results of this study are in agreement with those of Jaffe (16).

(16) *Arch. of Path. & Lab. Med.*, 5:13-22,  
Jan., 1928.

We observed that the size of the granules remained somewhat larger in older individuals in instances of exophthalmic goiter just as they do in normal thyroids of corresponding age. In these instances the amount, duration, and method of iodine therapy appears to have played no specific role in influencing the size, character, and distribution of lipins, except in so far as it produced a recession of activity and established stability of epithelium. The disappearance of fat from the supportive stroma was most likely due to generalized increased metabolism. The sudanophil content of the blood vessels and the absence of any stainable substance in the lymphatic channels may possibly point to the manner of dispersion of the hormone. Especially if one can assume that the presence of lipins in the various types of functioning cells are associated with hormone production.

#### DISCUSSION

It is noteworthy that in this series of primary hyperthyroidism, there appears to be an increase in the number

## HISTO-PATHOLOGY GROUP I

ACINI												STROMA										ABNOR. Degree
Acc. No.	Iodine Amt.co	Size		Colloid		Epithelial						Increase		Round Cells			Lymph V.		Blood V.			
		F.	G.	Amt.	Cond.	Hv-pl.	Hv-tr.	Inf.	F.	G.	F.	G.	F.	G.	Nodes	Dil.	Eng.	F.	G.			
14581	2	"	S	FA	GH	2	0	0	2	0	0	2	3	2	1	0	2	0	1	0	2	
17729	1	S	U	FA	LV	4	2	4	2	3	0	0	1	2	2	0	3	0	2	0	3	
14186	4	L	S	FA	LV	3	0	4	0	3	2	3	1	2	0	2	2	0	1	0	3	
13624	12	L	S	FA	GH	2	0	4	0	1	0	0	2	3	1	0	2	0	0	0	2	
13663	24	S	L	FA	LV	2	3	0	3	3	0	4	3	0	2	0	2	0	2	0	3	
13908	14	S	L	S	GH	1	0	1	0	0	1	0	2	0	1	0	1	0	1	0	1	
14211	13	S	L	A	GH	2	0	2	0	1	0	2	1	2	0	0	1	0	1	0	1	
15569	8	"	S	S	FEL	0	2	0	2	1	1	4	2	4	1	0	3	2	3	2	3	
17715	5	S	"	"	GH	1	0	2	0	1	0	2	0	1	0	0	2	0	1	0	1	
13568	10	S	L	LCYS	FV	1	0	2	0	2	0	2	0	4	0	2	1	0	0	1	1	
17302	3	S	"	"	GH	1	0	1	0	0	0	2	1	1	0	0	0	2	2	0	1	
14047	4	S	L	A	GH	2	0	2	0	0	0	3	2	2	0	0	1	0	1	0	1	
14705	72	S	L	A	GH	3	0	3	0	2	0	3	0	1	0	0	2	0	1	0	2	
14661	1.5	S	S	S	FV	2	1	3	3	0	0	2	1	3	2	0	2	0	0	2	2	
16535	2	S	S	S	FV	3	2	3	2	3	2	4	3	2	3	0	0	3	0	2	3	
15055	20	S	L	A	FV	2	0	3	1	2	0	3	2	1	0	0	2	0	1	0	2	
17265	3	S	"	"	FV	2	0	2	0	1	0	2	0	0	0	0	2	1	2	1	2	

Chart IX. Illustrating the manner of study of all of the 131 instances. Similar charts of groups II and III are not included in order to conserve space.

Key to abbreviations:-- (1) Size: L--Large; M--Medium; S--Small; U--Undifferentiated;

(11) Colloid: (A) Amount: S--Scant; M--Moderate; A--Abundant; LCYS--Cystic dilatation of acini--large cysts; FA--Focal absence; FC--Focal collections; LP--Large pools--(acini ruptured);

(B) Condition: FV--Focal vacuolization; GH--Generally homogeneous; FEL--Focal epithelial inclusions; (111) Epithelium: (A) Hy-pl.--Hyperplasia; F 1,2,3, or 4--Focal and Degree; G 1,2,3, or 4--General hyperplasia and degree; FS--Focal solid;

(B) Hyp-tr.--Hypertrophy: F 1,2,3, or 4--Focal and degree; G 1,2,3, or 4--General and degree; (C) Inf.--Infolding; F 1,2,3, or 4--Focal and Degree; G 1,2,3, or 4--General and Degree.

developing at an earlier age than has been previously observed by us. Whether this is due to over use of iodine given prophylactically or therapeutically was not learned from our records. There is a suggestion that such injudicious uses may play a role. On the other hand it is our experience that the extreme degrees of toxicity are less frequently found since an attempt has been made to establish the required amount of iodine in the food

content. Yet Liek (17) and others (17) *Müncher Med. Wochenschrift*, 74:1786 (Oct.) 1923.

seem to think that endemic goiter is increasing by such prophylactic use of iodine. In this clinicopathological study we were, however, concerned with the possible effect of iodine as a prophylactic agent in goiter prevention only in so far as it may have induced hyperthyroidism for which we now

use iodine in the therapy or in so far as it may modify such action from a clinical standpoint.

The clinical changes accomplished by the use of iodine in carefully selected instances of primary hyperthyroidism are generally recognized. They consist of a temporary abeyance of most of the usual manifestations with the exception of the exophthalmos which persists for a considerable period of time and often remains permanent. The pulse rate drops, the basal metabolic rate decreases and the nervous symptoms become less. This improved clinical state varies in degree and time, but is usually of short duration.

Opposition to the use of large amounts of iodine in the therapy has been expressed by a number of writers. Marine (*vide supra*) spoke sarcastically of the utilization of massive doses as the "iodine flood". In our procedure the average daily dose was 152.9 mgm., an amount in excess of that recommended by Marine. We were not able to establish any serious effects of such doses over a short period of time after a most careful clinical and pathological study. In most instances the amount of iodine used actually appeared to give definite clinical results. It may be true, however, that smaller amounts given over a more carefully determined period might give more permanent results. It seems to us that this effect of iodine dosage in a specific instance depends upon the status of the gland at the time it is administered. As has been previously pointed out the thyroid undergoes varying degrees of remission and progression in its activity and that the

clinical symptoms of hyperthyroidism lag during these cyclic changes. Therefore the effect of the administration of iodine will depend upon the extent of the natural involution already in progress and variable dosages will under such conditions produce dissimilar effects. Inasmuch as the role of iodine is apparently concerned with intra-acinar colloid accumulation much depends upon the direction of the polarity of the cell at the time the iodine reaches the gland. It follows that if colloid storage is already in progress less iodine would be required than if the progressive secretory momentum of cells were still to be overcome. So that since it is impossible to accurately determine the exact secretory state of the gland, large doses may actually increase the negative phase of areas undergoing inversion, and have a diminished effect upon areas that are still irritably hyperplastic or leave them uninfluenced. The foregoing is of course an assumption based upon the idea that the action of iodine is largely a matter of physical chemistry stimulating colloid production and by secondary increased intra acinar pressure, ironing out the hyperplastic infolding, and finally inhibiting the secretory power of the epithelium. On the other hand massive doses may abruptly halt the secretion and determine a properly timed surgical intervention.

Following iodine therapy the amount of the gland to be removed still remains a question of symmetry and the individual surgeon's judgment. It is necessary from the surgical point of view, in these cases of primary hyperthyroidism influenced by iodine, to take

into consideration several factors: (1) The age of the patient; (2) The duration of the condition; (3) The severity of the symptoms; (4) The amount of iodine given, and the rapidity of response to it; (5) The fact that a certain amount of hyperplasia will recur in the remaining stumps. It has been our policy to wait for the stabilization of clinical symptoms and then remove as much as possible in order to avoid recurrences. In a considerable number (8 to 10%) there may follow a period of hypothyroidism but at the time of operation this occurrence cannot be foretold so that its possible development must be temporarily ignored. The postoperative excess hyperplasia was controlled with further small doses of iodine, the postsurgical effect of which has been pointed out by the experiments of Halstead (*vide supra*), Marine (*vide supra*), Loeb (18) and Else (19). The temporary

(18) *J. Med. Res.* 40:199-255, July, 1919.

(19) *J. A. M. A.*, 89:26, 2153 Dec., 1927.

hypothyroidism was counteracted by the use of desiccated thyroid. The end results of such a detailed rationale in the therapy can only be determined by a careful follow-up record of patients so treated. This phase of the study is being continued.

In recent studies of the pathological changes produced by iodine in instances of primary hyperthyroidism Cattell (20), Giordano (21), Sager (*vide supra*) and Rienhoff and Lewis (22) and others have in general agreed

(20) *S. Clin. N. Amer.*, 6:597, 603, June, 1926.

(21) *Arch. Path. and Lab. Med.*, 1:881-888, June, 1926.

(22) *Arch. of Surg.*, 16:1, 79, Jan., 1928.

upon the effect of iodine, namely, that it causes a recession of activities with the accumulation of colloid and a general reduction in the vascularity. Microscopically the essential changes noted have to do with progressive development of intra-acinar colloid with a pushing back of the hyperplastic projections and the establishment of more uniformity in the size and regularity of the acini. Similar changes were found by one of us (Menne) in the glands of this series. There was no consistency in the relationship of the changes to the amount of iodine administered. In general the longer iodine was administered the greater was the accumulation of colloid. But in some instances in which iodine was used for a single day, large pools of colloid were seen. These were probably remnants of a previous state of inversion. On the other hand in some of the glands of patients treated with iodine over a long period of time (175 days) discrete hyperplastic foci occurred. In these instances, collections of small acini with hyperplastic epithelium were observed lying between those bulging with colloid. This may be assumed to be a response, on the part of the gland, to stimuli for more hormone, in the presence of the depressing effect of iodine produced colloid storage. Round cell infiltration is so variable in its character and distribution that its real significance cannot be determined, except that it may be concerned with removal of the by-products of cell metabolism in the fabrication of the hormone or accompany a more definite chronic lymphangitis.

No marked variation in the histopathology occurred in the three groups

and there is no particular advantage in such a division. Beneath the various patterns resulting from primary hyperthyroidism influenced by varying amounts of iodine in the therapy, one can still see evidence of the usual physiologic spotty activity, the changes induced by remissions and progressions following unusual demands, and the scars wrought by advancing age and other diseases. The full role of iodine, while illuminated by the work of Kendall and Harrington as to its specificity in the hormone, still remains hidden in the mass action evidenced in its valuable clinical use.

#### CONCLUSIONS

(1). The effect in an endemic area of iodine in the therapy of primary hyperthyroidism occurring in patients over a wide age variation (15 to 69 years) is given.

(2). The study of such instances according to groups based upon age and the periods of puberty, adolescence, menopause and post-menopause, while interesting offers no particular advantage. The essential differences between the clinical and pathological manifestations in these three groups are not marked.

(3). An increased vascular tension irrespective of age or arterial disease is evident.

(4). The clinical symptoms of primary hyperthyroidism in general are less severe since the prophylactic use of iodine, while there is some evidence of an increased number of cases requiring supervision and observation.

(5). Iodine in the therapy temporarily allays the symptoms and stab-

ilizes metabolism, but is limited in maintaining such a balance.

(6) Massive doses followed by properly timed surgical interference have given satisfactory immediate results, but the permanency and real value require a follow-up study.

(7). It is advisable to remove as much gland as possible and to control the temporary postoperative hypo- or hyper-activity with well chosen doses of desiccated thyroid or iodine respectively.

(8). The average amount of the gland removed in this series exceeded the average weight of the entire adult gland.

(9). The gross and histologic changes found here are in accord with those of other investigators. Intra acinar colloid storage with a physico-chemical and mechanical inhibition of secretory function and power is probably as important as an explanation of iodine action as the complete iodination of the hormone.

(10). The nature and distribution of sudanophilic substance suggests a marked cellular metabolic disturbance associated with hormone fabrication.

(11). On the basis of the histologic study it was possible to determine that all of the glands had undergone some change. In 76% of the glands at least a 50% inversion occurred following the preoperative use of iodine.

(12). The permanency of the efficacious use of iodine can only be determined by more experimental studies of its real role in colloid storage and checking of the metabolic constancy of patients so treated.

## Editorial

### *The Spread of Broad Tapeworm Infestation Throughout the United States.*

Within the last twenty years there has occurred a most interesting increase in the incidence of broad tapeworm (*Diphyllobothrium latum*) infestation throughout the United States, to such an extent that this parasite must be now regarded as of both medical and economic importance in this country. In 1895 very few human cases of infestation with this tapeworm had been seen in America, and such clinical rarities were confined to their occurrence in immigrants from the Baltic region, Finns especially bringing with them from their homeland one or more specimens in their intestines. Wherever a large aggregation of Finnish immigrants was concentrated, specimens of this worm were sooner or later reported. In Michigan, particularly, the large Finnish population in the Copper Country provided numerous specimens of this worm. For some years these specimens were all naturally regarded as imported in the bodies of their hosts. Since known infestations extending over fourteen years had been reported from Europe, it was not considered safe to regard this infestation as indigenous until the parasite was found to be harbored by a native-born American. That such indigenous cases must sooner or later

appear seemed inevitable. The stage was fully set for the appearance of native Americans infested with the broad tapeworm, and who, never having been out of their native land, had acquired the parasite at home. The large body of Finns in the Great Lakes Region who must harbor the fish tapeworm, since they came from a country in which such human infestation with this worm is variously estimated at from 20-40 per cent; the discharge into the waters of the Great Lakes of sewage containing great numbers of ova of this worm, and the favorable conditions for the life and development of these ova into free-swimming embryos and their plerocercoid stages in the fish of these lakes made it no difficult or improbable prophecy, as early as 1897, that this parasite was certain to become indigenous in these waters. By 1911-12 this had already occurred. Native cases had already been reported from Minnesota and Michigan. Then in 1911-12 fish obtained from Portage Lake examined at the Pathological Laboratory of the University of Michigan were found to have typical fish tapeworm plerocercoids in them, and the fact that this parasite had established itself in American was demonstrated. Since that time an increasing incidence in the number of specimens of the broad tapeworm sent into various pathological laboratories throughout the country has occurred. Not only is this



true of the Great Lakes region, but personal communications from laboratory men in the East, particularly in New York, bear this out. In one large diagnostic laboratory in the latter city, it is stated that fifty per cent of the tapeworms brought in are now of the broad form. Of still greater interest is the fact that today most of the infested patients are native Jews, instead of the Finnish or Swedish patient of 15-20 years ago. In Michigan the broad tapeworm cases now come from the industrial towns in the lower portion of the state, instead of from the Upper Peninsula as they formerly did. Detroit now furnishes the great majority of these cases, and the patients so infested during the last five years have all been Jews. This opens up new and very important lines of investigation. It is very evident that fish infested with the broad tapeworm are now in the markets of our large cities, and that the consumption of these in an uncooked or imperfectly cooked state must be responsible for the increasing incidence. It is, therefore very important to discover the source of these infested fish, and to issue proper warning as to their use. As far as some of the cities are concerned, the majority of the fish appearing in the markets are from northern lakes; and in the case of pike and pickerel are brought in from Canadian waters. Lake Winnipeg has been shown by Magath to be another endemic focus of infestation of the fish. It is interesting that the fish brought to the large markets for the Jewish trade are brought in unfrozen, and are used for food uncooked. Such fish sell at a certain premium as far as the Jewish trade is concerned. We are,

therefore, in possession of all the links in the chain of knowledge explaining the increase in the incidence of human infestation with this parasite, and the change in the racial type of host, from Finn to Hebrew. As to the species involved the plerocercoids have been found chiefly in pike, pickerel and burbot. The last named is not likely to appear in the markets; of the others the walleye pike is probably the most common source of the infestation. No plerocercoids have been found in white fish. Nevertheless, the safest rule will be to eat no fish from northern lakes that have not been thoroughly cooked. Educational warnings should be given against the eating of raw fish. Salting, drying and ordinary curing do not kill the plerocercoid. As to the injurious effects in the host of the broad tapeworm a marked individual susceptibility must occur. In Finland only a small percentage of those harboring the adult tapeworm show any well-marked clinical symptoms. These are of the nature of an anemia, which may vary greatly in degree, from that of a simple secondary anemia to severe types resembling pernicious anemia. After expulsion of the worm recovery is usually rapid and complete. It is also of importance to know that liver diet results in rapid restoration of the blood picture to the normal, even when the worm is still present in the intestine. The pathology of fatal cases presents the picture of a severe hemolytic anemia, practically identical with that of pernicious anemia, except in the tract degenerations of the spinal cord. Glossitis, hemosiderosis of liver and other organs, marked atrophy of the mucosa of stomach and intestine,

fatty degenerative changes in myocardium and liver, with megaloblastic or exhausted bone marrow are found in the severe cases. Every case of anemia coming for treatment should have careful and repeated stool examinations made for ova or segments of this worm. The percentage of infested cases without symptoms to those showing anemia is high, so that to every infested patient with the latter symptom there are many who have the worm but present no symptoms (1-2 per cent only of those infested show anemia according to Faber). Treatment is easy and simple. It must be borne in mind that often more than one worm is present, and that careful search should be

made for the head or heads. It is unfortunate that such a parasite should have been allowed to become established in this country. The proper disposal of sewage from our towns and villages would, in the first place, have prevented such an infestation of our food fishes, but in the existing stage of our civilization such was an impossibility, so, although cognizant of the situation and its possibilities, we have been obliged to wait and see slowly but surely realized the fulfillment of the prophecy made more than thirty years ago. As in so many other instances our knowledge outruns our ability to act upon such knowledge.

## Abstracts

*Sex-Differences in Heart Action. I, Duration of Systole; II, Heart Rate.* By W. P. Lombard and O. M. Cope (Amer. Jour. of Physiology, December, 1927).

An examination of the curves of the duration of systoles in men and women, in recumbent, sitting and standing positions, with respect to cycle lengths, these being plotted as abscissae and systole lengths as ordinates, show that systoles in all positions progressively shorten as cycle lengths decrease. As cycle lengths shorten (pulse rates increase) not only is there less time for venous blood to accumulate, but the blood is pumped out of the veno-auricular reservoir more rapidly, and the systoles become shorter and shorter as the cycles decrease. The systoles are longer in the recumbent position than in sitting, and in sitting than standing, for like cycle lengths, because gravity retards the flow of venous blood in increasing proportion as the position approaches the horizontal. The relative pitch of the three curves indicates that as the cycle lengths decrease the systoles shorten less rapidly, also as the position becomes more horizontal. In long cycles (slow rates) there is time for the blood to get back to the heart in spite of the retarding effect of gravity in the standing and sitting positions; but as cycles shorten, gravity has a relatively greater influence, and although the effect of short cycles on the accumulation of venous blood is to be seen in all positions, it is more marked in the sitting and still more so in the standing curve. Although the curves of men and women show that the systole lengths respond in general in like manner to the effects of heart rate they respond in different degrees. The systoles of women are longer than those of men for like cycle lengths in all positions. The rate of the fall of the curves of women is different from those of men and this

difference varies with the position. It is suggested that the difference between the sexes may be due to the hearts of women being smaller in comparison with their size than those of men. If this is true it would explain why the effects of gravity and of changes in cycle length would be greater in the case of women than men. The study of the heart rate in men and women shows that women's hearts beat faster than men's in all positions studied. The pulse of women does not slow as much as that of men as the position becomes more horizontal. Differences in rate between men and women are greater as the rates compared are more rapid. The systoles of women are uniformly longer than those of men at the same cycle length and position. The systoles of women do not lengthen to the same degree as those of men as the position approaches the horizontal. The greater the difference in the pulse rate of women as compared with men, the less is the difference in the length of the systoles. As cycles lengthen, the systoles of men lengthen more than those of women, and the pulse rates decrease more, except in the case of the recumbent position in which the rates are all very slow, and so approach each other. As the position approaches the horizontal, the lengthening of systoles and decrease of pulse rates are in both cases greater for men than women. The explanation of these differences in pulse rates in the two sexes, as in the systoles lengths, may be that the hearts of women are smaller in proportion to the size of their bodies than those of men. The hearts of women maintain a higher rate to compensate for the larger amounts of blood they have to pump in relation to their size. The hearts of women compensate for their sex-difference either by a relative increase of rate or a lengthening of the systole. The faster pulse rates of women are accompanied

by relatively longer systoles, and it suggests itself that these faster rates constitute a compensatory phenomenon, which shortens the systoles of women.

*Two Years' Experience with the Malarial Treatment of General Paralysis in a State Institution.* Clinical, Serological and Autopsy Observation in 100 cases. By Max A. Bahr and W. L. Bruetsch, Central State Hospital, Indianapolis, Indiana (Amer. Jour. of Psychiatry, Vol. VII, March, 1928, p. 715).

Of 100 general paralytic patients treated with malaria, 25 were able to leave the hospital. Twelve patients improved to such a degree that they can be trusted in an useful occupation in the hospital. Forty patients are placed in the unimproved group. In 32 patients of the latter group the disease is progressing. In 8 instances the disease has remained stationary. Five patients succumbed during the rigors and 18 died following the malaria. Serological changes following malarial treatment occurred in both the improved and the unimproved groups. While there was no parallelism between the degree of clinical and serological improvement, particularly as far as the colloidal gold curve was concerned, it was higher in the improved groups. The paretic gold curve was reduced in intensity but remained of the paretic type. Then conversion of a paretic curve into a true luetic one in our cases was an exception. The method of the treatment of general paralysis with malaria is relatively simple, compared with the other methods and can be easily carried out in a state institution. It cannot be denied that this form of treatment is attended with definite risk for the patient. With a better knowledge of the complications that arise during the rigors, death due to therapeutic malaria will be reduced. If, on the other hand, one reviews the fatalities occurring in the course of the specific treatment, particularly with the intraspinal methods, one is aware that no treatment is without hazard. Of the five patients who died during the malaria, the immediate cause of death in two cases was malaria, one died of splenic rup-

ture, one developed a pneumonia, and in one instance death was caused by paralytic seizures. In the 18 cases dying following the malaria, death took place from 2 weeks to 18 months after the treatment. Those who died shortly after the treatment (2 weeks to 2 months) were advanced cases of over 2 years standing. Those patients did not recover from the malaria, they failed to regain the weight which they had lost during the rigors and were rapidly going down-hill after the cessation of the malaria, some with the development of trophic ulcerations. In these advanced cases it seemed that death was hastened by the inoculation. In some instances a slight physical improvement was noted. This was only of a short duration and not accompanied by a mental improvement. Two cases of this group deserve notice, one, a paralytic, who died of a splenic abscess 7 weeks after the paroxysms were stopped, and the other was a patient inoculated from this case, who showed at autopsy a verrucose endocarditis of the mitral valve, hemorrhagic infarction of the spleen and areas of embolic softening in the brain. This case shows clearly that the present method of direct transmission of blood from patient to patient is not without danger, as the donor may be the carrier of latent disease germs which may be transferred together with the malarial plasmodia. To avoid such unfortunate accidents the more complicated method of inoculation by *Anopheles* as elaborated by English authors could be employed.

*The Active Principle of the Posterior Lobe of the Pituitary Gland. I, The Demonstration of the Presence of Two Active Principles; II, The Separation of the Two Principles and Their Concentration in the Form of Potent Solid Preparations.* By Oliver Kamm, T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Brybee (Jour. of the Amer. Chem. Soc., 50, 573, 1928).

The manifold physiological activities of extracts of the posterior lobe of the pituitary gland are now well known: namely, their effect in stimulating uterine contractions (oxytocic activity), their ability to raise the

blood pressure (pressor activity) and their diuretic-antidiuretic effects (renal activity). These three types of activity have led the way to three definite and important medical applications; these are illustrated respectively by the use of pituitary solutions in obstetrics, in the treatment of surgical shock, and in the control of diabetes insipidus. On the other hand, chemical information concerning the physiologically active constituents of pituitary extracts is rather meager; in fact it has not been shown definitely whether the above enumerated pharmacological activities are due to a single chemical substance (hormone) or to the presence of several different compounds. The American investigators, and this is true especially of the Johns Hopkins and the U. S. Hygienic Laboratory groups, have defended the evidence favoring a single active principle, whereas the English workers have argued for two or three principles, while the Germans at one time claimed the separation of even a larger number. The present investigation has been successful in obtaining two fractions differing from each other when subjected to the two acceptable quantitative assay methods; these two principles have been obtained in the form of stable, highly potent, water-soluble powders. By recombining the fraction in the original proportions a pituitary solution indistinguishable from the original is again obtained, thus proving that no injury of any active principle has taken place. The authors summarize their work, as follows: The posterior lobe of the pituitary gland contains two important active principles; one which raises blood pressure and another which stimulates contraction of uterine muscle. A substantially complete separation of these two active principles has been accomplished by the employment of salting-out methods, and,

subsequently, by the use of appropriate solvents and precipitants. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (B-hypophamine) has been obtained in the form of a white, stable, water-soluble powder 80 times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (A-hypophamine) has been obtained in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Standard Powdered Pituitary. The pressor principle has been found to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles are basic bodies presumably amines. Practical manufacturing methods have been developed for the separation of these two hormones, and they have been made available to the medical profession for careful clinical trial. As a result of this preliminary work the foundation is now laid for an investigation of the chemical nature of the separated hormones of the posterior lobe of the pituitary gland, together with a more exhaustive study of their pharmacological properties. While additional purification may raise the potency values above those reported here, and it is probable that ultimately these two principles will be secured in crystalline form, such purification is not essential to the successful clinical application of these two new products.

## Reviews

*The Diagnosis of Congenital Cardiac Disease.* Part I, The "So-called Acyanotic" Cases, By Maude E. Abbott, M.D., and Edward Weiss, M.D., Philadelphia; Part II, True "Morbus Caeruleus." By Maude E. Abbott, M. D., McGill University, Montreal. Blumer's Bedside Diagnosis, II, 353-514. W. B. Saunders Co., Philadelphia, 1928.

A thorough knowledge of congenital cardiac anomalies is essential to every internist, for, no matter how infrequent these lesions may be, if one is to stand on safe ground in the differential diagnosis of heart disease, he must have an understanding of the circulatory and respiratory phenomena associated with such disturbances of development of the heart. Such an understanding has a practical clinical value far out of proportion to the relative frequency of cardiac anomalies. The study of the circulatory and respiratory signs and symptoms produced by such defects, which are the result of the interaction of simple physical laws, gives a knowledge essential to a solid foundation in the broader field of general cardiology. There is probably no part of cardiac pathology, symptomatology and prognosis so little known to the general practitioner as that of congenital heart disease, and many cases of such go unrecognized or incorrectly interpreted. This failure is, of course, of immense importance to the unfortunate patient, and this is particularly true of that larger and clinically much more important group of congenital cardiacs who possess anomalies giving slight or latent symptomatology, but compatible with a relatively good expectancy of life provided they do not meet with accidents or intercurrent complications precipitating a breakdown at the site of cardiac weakness and strain. The number of these congenital potential cardiacs is probably very much greater than is usually supposed, and pre-

ventive medicine is concerned with their early recognition and the proper preventive care that should be accorded to every potential cardiac case. Up to very recent years the average treatment of the subject of congenital cardiac lesions in textbooks of internal medicine has been very unsatisfactory, and the clinical differentiation of the different types unnecessarily obscure. The average internist avoids the paragraphs bearing upon congenital cardiacs as nuisances too rare and unpractical to be worthy of consideration or understanding. He will waste no time upon them. This attitude of mind is true to some extent even of some of those who pose as cardiologists, or at least, lay claim to a more superior knowledge of cardiac disease. Therein a fundamental error is committed; for the problems of cardiac congenital lesions are mechanico-physical ones, embracing the whole fundamental anatomy and physiology of the circulation; and the elementary knowledge of the normal development of the heart, its normal anatomical structure and its normal physiology makes understandable the deviations due to prenatal disease and disturbances of embryonic development. The difficulty which most physicians have of visualizing the anatomical changes and the resulting disturbances of the circulation will disappear with a knowledge of the anatomical nature of the defect and its resultant disturbance of the circulation. This knowledge is concentrated in Dr. Abbott's book as it is in no other work on the heart. A clear picture of the possible anatomical condition existing is given, and then a logical classification of the various clinical types of congenital cardiac disease. This classification is based upon the pathologicophysiological conditions of the circulation imposed upon it by the new conditions produced by the defect. In this clinical classification Dr. Abbott follows Bamberger who taught

that cardiac anomalies should be classified according to the presence or absence of mechanical interference with the oxygenation of the arterial blood, that is, the presence or absence of congenital cyanosis. From this point of view three classes of congenital heart lesions may be recognized: I, the Acyanotic Group, comprising such cases as coarctation of the aorta and other left-sided lesions in which no abnormal communication between the two circulations exists, and in which, therefore, there is no cause for congenital cyanosis; II, Cyanose Tardive, cases in which a communication does exist, in the form of a localized interauricular, interventricular or aortic septal defect or a patent ductus arteriosus, but without other complication, so that under the normal conditions of the circulation, in which pressure is higher on the left (arterial) side the intracardiac or intra-arterial current is of the nature of an arterial-venous shunt. Here there is also no reason for cyanosis, unless the direction of the current is reversed by a pathological rise of pressure in the right heart or pulmonary artery producing a temporary or permanent reversal of flow, with a resultant transient or terminal cyanosis; III, Cyanotic Group (*Morbus caeruleus*) comprises all those cases in which the oxygen-unsaturation of the capillary blood is raised above its threshold value for the appearance of cyanosis (placed by Lungs-gaard at 6.7 volumes per cent). Permanent cyanosis inevitably results from the direct admixture of venous blood with the arterial (venous-arterial shunt), comprising such lesions as septal defect with associated anomalies of right heart which raise the pressure above that on the left side, dextra-posed or transposed aorta, biloculate and triloculate heart and persistent truncus arteriosus. Based upon this clinical classification Dr. Abbott gives a masterly description and analysis of cases falling into these three groups. Her book is the most complete exposition of the whole subject of congenital heart disease, and from it the practitioner will be enabled, as in no other way, to visualize the anatomical structure of cardiac disturbances of development and their pathological physiology and symptomatology. He will thus be able to diag-

nose such lesions, and advise intelligent treatment and care. Further, his foundation for a broader cardiology will be immensely strengthened.

*Cavernous Sinus Thrombophlebitis and Allied Septic and Traumatic Lesions of the Basal Venous Sinuses.* A Clinical Study of Blood Stream Infection, By Wells P. Eagleton, M.D., Newark, N. J., Medical Director, Newark Eye and Ear Infirmary, Newark, N. J., Chief of the Division of Head Surgery, Newark City Hospital; Consulting Craniologist, St. Barnabas' Hospital, St. Michael's Hospital, Memorial Hospital, Beth Israel Hospital of Newark, N. Y.; Orange Memorial Hospital, Orange, N. J.; Muhlenberg Hospital, Plainfield, N. J.; and Mountainside Hospital, Mountclair, N. J. 196 pages, 17 figures and charts. The MacMillan Company, New York, 1926. Price in cloth, \$3.00.

This monograph is the record of the author's personal experience in which he reviews his cases at length, placing special emphasis upon each and every diagnostic or operative error made. As he has learned chiefly through his failures he has laid especial stress upon these, so that others may profit from his experience. Inasmuch as thrombophlebitis of the cavernous sinus has up to the present time almost uniformly terminated fatally, he is persuaded that a study of the included cases will enable a diagnosis to be made early enough for rational surgery to be effectual, in a certain proportion of cases. His material consisted of 25 personally studied cases of cavernous sinus thrombophlebitis with 21 deaths and 4 recoveries. The chief object of this study is to emphasize the importance of the following considerations in the diagnosis and treatment of infective cavernous sinus disease. If the diagnosis is to be made early, which it must be if surgical intervention is to have the slightest chance of success, cavernous sinus phlebitis must be regarded as a group of diseases. For early diagnosis it must be appreciated that the classical symptoms of exophthalmos, edema of the lids and chemosis may or may not be present, depending on whether the sinus is sud-

denly and completely obstructed by an acute septic process, or gradually obliterated by a thrombus. An early diagnosis in the cases of slow involvement without classical symptoms of exophthalmos (the most promising type for surgical intervention) necessitates a careful study of the following mechanical factors which determine the symptomatology: (a), The path of entrance of the infection into the sinus; (b), the part of the sinus first attacked; (c), the alterations in the adjacent tissue that occur as the result of the venous anastomosis of the sinus. Finally, the necessity must be emphasized of placing the inflamed radicle at rest by ligation of the common or internal carotid artery, as well as treating the phlebitis by drainage. As to the frequency of cavernous sinus thrombophlebitis less than 300 cases had been recorded in the literature up to 1918; but it is very probable that it is not so infrequent if carefully sought for in septicemia and pyemia during life, or at autopsy following general blood stream infection. It must be realized that a septic clot may fill the cavernous sinus of both sides, the only symptom present being high, continuous temperature or chronic sepsis. The route of infection into the sinus may be ophthalmic, pterygoid, sphenoidal, aural, tonsillar, and carotid venous plexus. Mixed types may occur. Each of these six types may or may not present the classical localizing symptoms of cavernous sinus thrombosis, in exophthalmos and chemosis, depending upon whether or not the circulation in the cavernous sinus is suddenly and completely occluded. Of particular importance to the general practitioner is the etiological relationship of operative trauma to cavernous sinus involvement and death, as in the case of staphylococcal furuncles and carbuncles of the face, particularly of the lip and nose. In these cases early operative incisions and squeezing in the early stages not only frequently fail to reveal pus in the furuncle, but have been followed by a rapid extension. Through dissemination of the bacteria the surgeon converts a local process into a general blood stream infection, which through a retrograde thrombophlebitis of the angular and facial veins, causes cavernous sinus involvement and death. Al-

though this monograph deals with a highly specialized surgical procedure, the clinical aspects, as in the type just mentioned, are of the greatest importance to the practitioner, who usually is the one who sees the beginning of the infections leading to the involvement of the cavernous sinus, and, therefore, the basic knowledge herein contained should be familiar to him, so that he may make no diagnostic errors. The case histories contain much interesting and valuable material.

*A Textbook of Biologic Assays.* By Paul S. Pittenger, Ph.G., Ph.C., Ph.M., Phar.D., Instructor in Biologic Assaying, Philadelphia College of Pharmacy and Science, Philadelphia and Temple University Department of Pharmacy, Philadelphia; Member of the General Committee of Revision, Member of Subcommittee on Biological Assays, and Member of the Subcommittee on Biological Products and Diagnostical Tests of the Pharmacopoeia of the United States of America; Director of Pharmacological Research Laboratories of Sharp and Dohme; Chairman of the Physiological Testing Committee of the American Pharmaceutical Association; Member and Former Vice-President of the American Pharmaceutical Association; Chairman of the Committee on Pharmacology and Biologic Assays of the National Conference of Pharmaceutical Research. 373 pages, 153 illustrations, P. Blakiston's Son and Co., Philadelphia. Price in cloth, \$3.00.

The first edition of this book was published in 1914; and at that time the subject of Biologic Assays was taught in very few Colleges of Pharmacy or Medicine, and was not recognized by the United States Pharmacopoeia or the National Formulary. At that time only a few experts engaged in the larger laboratories devoted to drug standardization were being employed in this work. The only official recognition previous to 1914 was taken by the United States Pharmacopoeial Convention of 1910 in recommending to the Revision Committee "that biologic tests or assays, when accurate and reliable may be admitted" to the U. S. P. IX. This recommendation resulted in the



that cardiac anomalies should be classified according to the presence or absence of mechanical interference with the oxygenation of the arterial blood, that is, the presence or absence of congenital cyanosis. From this point of view three classes of congenital heart lesions may be recognized: I, the Acyanotic Group, comprising such cases as coarctation of the aorta and other left-sided lesions in which no abnormal communication between the two circulations exists, and in which, therefore, there is no cause for congenital cyanosis; II, Cyanose Tardive, cases in which a communication does exist, in the form of a localized interauricular, interventricular or aortic septal defect or a patent ductus arteriosus, but without other complication, so that under the normal conditions of the circulation, in which pressure is higher on the left (arterial) side the intracardiac or intra-arterial current is of the nature of an arterial-venous shunt. Here there is also no reason for cyanosis, unless the direction of the current is reversed by a pathological rise of pressure in the right heart or pulmonary artery producing a temporary or permanent reversal of flow, with a resultant transient or terminal cyanosis; III, Cyanotic Group (*Morbus caeruleus*) comprises all those cases in which the oxygen-unsaturation of the capillary blood is raised above its threshold value for the appearance of cyanosis (placed by Lungs-gaard at 6.7 volumes per cent). Permanent cyanosis inevitably results from the direct admixture of venous blood with the arterial (venous-arterial shunt), comprising such lesions as septal defect with associated anomalies of right heart which raise the pressure above that on the left side, dextroposed or transposed aorta, biloculate and triloculate heart and persistent truncus arteriosus. Based upon this clinical classification Dr. Abbott gives a masterly description and analysis of cases falling into these three groups. Her book is the most complete exposition of the whole subject of congenital heart disease, and from it the practitioner will be enabled, as in no other way, to visualize the anatomical structure of cardiac disturbances of development and their pathological physiology and symptomatology. He will thus be able to diag-

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inclusion of several optional and two compulsory Biologic Assays in that Pharmacopoeia. During the period in which the U. S. P. IX was official the various biologic assays methods were improved to a point where it was considered advisable, in the interest of uniformity, to make a greater number of methods compulsory. In the U. S. P. X compulsory biologic assays were included for the following drugs and preparations: Aconitine, Aconite and its tincture, Cannabis and its fluid extract, Digitalis and its tincture, Strophanthus and its tincture, Solution of Epinephrine Hydrochloride and Solution of Pituitary. Since under the provisions of the Pure Food and Drug Act, the standards of the Pharmacopoeia and the National Formulary are made Law for Interstate Commerce in drugs and medicines, the necessity for teaching the subject of Biologic Assays in all Schools of Pharmacy

and Medicine is apparent. In the revision of this Manual, therefore, the wants of the pharmaceutical and medical colleges and their students have been the primary consideration. As in the first edition, methods familiar to experts but not referred to in the Pharmacopoeia or the literature with sufficient detail for students and beginners are fully described. It has been found necessary to rewrite practically the whole book, in order to include the many improvements in various methods, especially as to the technical details which have been developed since the first edition. This book should, therefore, adequately meet the present day requirements for a Textbook of Biologic Assays for students of Pharmacy and Medicine, and for those engaged in laboratories devoted to the biologic standardization of drugs.

## College News Notes

The next ANNUAL MEETING of the AMERICAN COLLEGE OF PHYSICIANS will be held in Boston under the auspices of the Harvard Medical School during the week beginning April 8, 1929.

Drs. Aldred Scott Warthin, W. McKim Marriott, John H. Musser, Clement R. Jones, George Morris Piersol, Sydney R. Miller, William Gerry Morgan, F. M. Pottenger, John A. Lichty, Leonard M. Murray, Alfred Stengel, James H. Means, J. C. Meakins, James Alexander Miller, James S. McLester, John Phillips, Charles G. Jennings, President Martin, and the Executive Secretary, Mr. Loveland were present at the Regents' Meeting held in Washington, April 29, 1928.

### *NEW METHOD FOR PROPOSAL OF MEMBERS FROM THE ARMY, NAVY AND PUBLIC HEALTH SERVICES*

At the New Orleans Session of the American College of Physicians, the Board of Regents adopted a resolution providing that candidates for membership from the Army, Navy and Public Health Services shall be proposed by the Surgeon General of each Service.

In establishing this method of proposal from these Services, it was thought that the Surgeon General will have at his disposal means of increasing morale and stimulating members of the Corps to better work. It is understood that there will be a limited number proposed each year from each Service, and that those selected will be men who have established a reputation for conspicuous ability and accomplishment or distinguished service as well as professional ability. Selection shall always be determined on the basis of professional merit and standing, character and reputation, and not necessarily on rank in the lineal list of medical officers. All candidates must meet the reg-

ular requirements prescribed by the Constitution and by the Committee on Credentials.

### FELLOWS ELECTED AT THE NEW ORLEANS MEETING

Alvarez, Walter Clement,	Rochester, Minn.
Arrasmith, W. W.,	Grand Island, Neb.
Balyeat, Ray M.,	Oklahoma City, Okla.
Bannick, Edwin G.,	Rochester, Minn.
Barborka, Clifford J.,	Rochester, Minn.
Bargen, J. A.,	Rochester, Minn.
Barrow, John V.,	Los Angeles, Calif.
Bealer, Frank Rudisill,	Washington, D. C.
Bell, Jess Vardeman,	Kansas City, Mo.
Berkman, David M.,	Rochester, Minn.
Bitzer, E. W.,	Tampa, Fla.
Bliss, Walter P.,	Pasadena, Calif.
Block, E. Bates,	Atlanta, Ga.
Blumer, George,	New Haven, Conn.
Bronfin, Isidor D.	Denver, Colo.
Brown, Thomas R.,	Baltimore, Md.
Busby, J. L.,	Rochester, Minn.
Chambers, Wilfred E.,	Kansas City, Mo.
Campbell, J. Watson,	Halstead, Kan.
Chapman, Lawrence Evans,	Galveston, Texas
Christian, Henry A.,	Boston, Mass.
Coeke, Chas. Hartwell,	Asheville, N. C.
Cole, James C.	New Orleans, La.
Conner, Lewis A.,	New York, N. Y.
Corley, Cecil,	Jackson, Miss.
Daley, Daniel Francis,	Kingston, Pa.
Davis, Kenneth S.,	Los Angeles, Calif.
DeLorme, M. F.,	Brooklyn, N. Y.
Dibrell, John R.,	Little Rock, Ark.
Diekens, Paul Frederick,	Washington, D. C.
Egan, William J.,	Milwaukee, Wis.
Emerson, Gouveneur V.,	Washington, D. C.
Falkowsky, Chas., Jr.,	Seranton, Pa.
Fenno, Frederick L.,	New Orleans, La.
Fontaine, Bryce W.,	Memphis, Tenn.
Foster, John H.,	Waterbury, Conn.
Freeman, Walter,	Washington, D. C.
Geer, Everett K.,	St. Paul, Minn.
Giffin, Herbert Z.,	Rochester, Minn.
Gilliland, Charles E.,	St. Louis, Mo.

Gingold, David,	Brooklyn, N. Y.	Norman, Estella G.,	Battle Creek, Mich.
Glidden, Edson W.,	Alton, Ga.	O'Malley, Mary,	Washington, D. C.
Goldsmith, Milton,	Pittsburgh, Pa.	Palmer, Walter W.,	New York, N. Y.
Greene, Carl H.,	Rochester, Minn.	Paullin, James Edgar,	Atlanta, Ga.
Greene, I. W.,	Owosso, Mich.	Peabody, Jos. Winthrop,	Washington, D. C.
Guthrie, J. Birney,	New Orleans, La.	Pearre, Albert Austin,	Frederick, Md.
Habein, H. C.,	Rochester, Minn.	Perkins, Orman C.,	Brooklyn, N. Y.
Haft, Henry H.,	Syracuse, N. Y.	Placak, J. C.,	Cleveland Heights, Ohio
Hall, David C.,	Seattle, Wash.	Plummer, William A.,	Rochester, Minn.
Hangarter, Andrew H.,	Brooklyn, N. Y.	Pomeranz, Maurice M.,	New York, N. Y.
Harris, Titus Holliday,	Galveston, Texas	Poust, Luther R.,	Fort Sam Houston, Texas
Hartley, German Smith,	Clifton Forge, Va.	Quinn, James H.,	Springfield, Mass.
Henderson, Walter F.,	New Orleans, La.	Rabinowitch, I. M.,	Montreal, Canada
Hoff, A. E.,	North Bend, Neb.	Rainey, W. T.,	Fayetteville, N. C.
Holbrook, Charles S.,	New Orleans, La.	Ramsay, Robert E.,	Pasadena, Calif.
Holmes, Paul McKinley,	Toledo, Ohio	Reye, H. A.,	Detroit, Mich.
Horn, William Sullivan,	Fort Worth, Texas	Roberts, George F.,	Salt Lake City, Utah
Houston, Wm. R.,	Augusta, Ga.	Root, J. Harold,	Waterbury, Conn.
Hunter, James E.,	Seattle, Wash.	Rowntree, L. G.,	Rochester, Minn.
Joslin, Elliott R.,	Boston, Mass.	Ryan, John G.,	Denver, Colo.
Kech, Augustus S.,	Altoona, Pa.	Sanford, Arthur H.,	Rochester, Minn.
Kemper, C. F.,	Denver, Colo.	Sauls, H. C.,	Atlanta, Ga.
Kinney, Lyell C.,	San Diego, Calif.	Sawyer, Carl W.,	Marion, Ohio
Kirk, William Wilson,	Jacksonville, Fla.	Schneider, Harvey C.,	Buffalo, N. Y.
Lambright, Geo. L.,	Cleveland, Ohio	Schonwald, Philipp,	Seattle, Wash.
Levy, M. D.,	Houston, Texas	Schottstaedt, W. E. Richard,	Fresno, Calif.
Libman, Emanuel,	New York, N. Y.	Schroeder, Frederick,	Brooklyn, N. Y.
Loewenberg, Samuel A.,	Philadelphia, Pa.	Sheppe, William Marco,	Wheeling, W. Va.
Longcope, Warfield T.,	Baltimore, Md.	Simon, Saling,	Denver, Colo.
Lorenz, Wm. F.,	Madison, Wis.	Simon, Sidney K.,	New Orleans, La.
Lotz, Oscar,	Milwaukee, Wis.	Sledge, Edward S.,	Mobile, Ala.
Luippold, Eugene J.,	Weehawken, N. J.	Smith, H. Mason,	Tampa, Fla.
Lyon, George M.,	Huntington, W. Va.	Smith, Morgan,	Little Rock, Ark.
Marbury, Charles C.,	Washington, D. C.	Smythe, H. S.,	Bristol, Va.-Tenn.
Marcovici, Eugene,	New York, N. Y.	Snader, Edward R., Jr.,	Philadelphia, Pa.
Marvin, H. Burns,	Binghamton, N. Y.	Sturgis, Cyrus C.,	Ann Arbor, Mich.
Mason, E. H.,	Montreal, Canada	Taussig, Arnold S.,	Denver, Colo.
McCants, John M.,	Philadelphia, Pa.	Taylor, Henry K.,	New York, N. Y.
McLean, C. C.,	Birmingham, Ala.	Taylor, Raymond G.,	Los Angeles, Calif.
McLester, James S.,	Birmingham, Ala.	Taylor, John C.,	Chelsea, Okla.
McNerney, Wm. J.,	Syracuse, N. Y.	Thayer, William S.,	Baltimore, Md.
Meakins, J. C.,	Montreal, Canada	Trossbach, Herman,	Bogota, N. J.
Means, James H.,	Boston, Mass.	Tucker, David Andrew, Jr.,	Cincinnati, Ohio
Meister, Wm. B.,	Fort Sam Houston, Texas	Ullman, Henry J.,	Santa Barbara, Calif.
Melson, Oliver C.,	Little Rock, Ark.	Verity, Lloyd E.,	Battle Creek, Mich.
Miller, Oscar O.,	Louisville, Ky.	Vischer, Carl V.,	Philadelphia, Pa.
Minot, George R.,	Boston, Mass.	Walcott, Harry D.,	Dallas, Texas
Montrose, Frank J.,	Buffalo, N. Y.	Waring, James J.,	Denver, Colo.
Mundy, Carl S.,	Toledo, Ohio	Watts, H. C.,	Fort Harrison, Mont.
Nesbit, William E.,	San Antonio, Texas	Webb, Gerald B.,	Colorado Springs, Colo.
Nice, Charles M.,	Birmingham, Ala.	Westcott, Leo Enos,	Kalamazoo, Mich.
Nichols, Estes,	Portland, Maine	Whinery, Joseph B.,	Grand Rapids, Mich.
Norbury, Frank Garm,	Jacksonville, Ill.	Williams, Lester James,	Baton Rouge, La.

Williamson, G. Richard, New Orleans, La.  
 Whipple, George H., Rochester, N. Y.  
 Woltmann, Harro, Mansfield, Ohio  
 Wuerthele, Herman William, Pittsburgh, Pa.  
 Yampolsky, Joseph F., Atlanta, Ga.  
 Yegge, W. Bernard, Denver, Colo.  
 Zemp, E. R., Knoxville, Tenn.

#### ASSOCIATES ELECTED AT THE NEW ORLEANS MEETING

Ayers, Samuel, Los Angeles, Calif.  
 Babcock, Edward S., Sacramento, Calif.  
 Barthelme, Francis, Olney, Ill.  
 Bishop, Louis F., Jr., New York, N. Y.  
 Blaisdell, Elton R., Portland, Maine  
 Butler, H. Wesley, New Orleans, La.  
 Colomb, Henry O., National Soldiers Home,  
 Va.

Coon, Harold M., Stevens Point, Wis.  
 Dunn, James N., St. Paul, Minn.  
 Emenhiser, J. L., Indiana Harbor, Ind.  
 Farnsworth, E. E., Grand Island, Neb.  
 Fife, Clinton D., Dayton, Ohio  
 Fisher, M. McC., Duluth, Minn.  
 Gamble, William G., Charleston, S. C.  
 Graves, Ghent, Houston, Texas  
 Hare, Herold P., Los Angeles, Calif.  
 Head, M. M., Zebulon, Ga.  
 Heninger, Ben R., Columbia, Miss.  
 Henry, Harvey R., Luling, Texas  
 Henske, Joseph A., Omaha, Neb.  
 Hill, Herbert, San Antonio, Texas  
 Horger, E. L., Columbia, S. C.  
 Howson, Carl R., Los Angeles, Calif.  
 Ireland, R. A., Charleston, W. Va.  
 Jaeger, Henry W., Washington, D. C.  
 Jeter, Hugh, Oklahoma City, Okla.  
 Krombein, Walter H., Buffalo, N. Y.  
 Leake, William H., Los Angeles, Calif.  
 Loomis, Edgar Webb, Dallas, Texas  
 Lounsberry, C. Ray, San Diego, Calif.  
 Maner, George, Los Angeles, Calif.  
 Matsger, Edward, San Francisco, Calif.  
 McIntire, Emery J., Carthage, Mo.  
 Miller, Tate, Dallas, Texas  
 Mogabgab, A., New Orleans, La.  
 Mowat, Kenneth G., Buffalo, N. Y.  
 Murphy, J. Harry, Omaha, Neb.  
 Otto, Frank W., Los Angeles, Calif.  
 Pigford, Russel C., New Orleans, La.  
 Pinney, George L., Hastings, Neb.  
 Reitzel, Raymond J., Galveston, Texas

Rohrbaeh, Harvey O., Bethlehem, Pa.  
 Rothschild, Karl, New Brunswick, N. J.  
 Sheppard, Thomas T., Pittsburgh, Pa.  
 Sites, Frank M., Louisville, Ky.  
 Susslin, Emil J., Bridgeport, Conn.  
 Waddell, James B., Indiana Harbor, Ind.  
 Wadsworth, John V., Buffalo, N. Y.  
 Ware, E. Richmond, Los Angeles, Calif.  
 Watson, Clyde E., Westwood, Calif.  
 Webster, John C., Los Angeles, Calif.  
 Wilson, R. E., Denver, Colo.  
 Winans, Leslie H., Ashland, Ky.

Dr. Hugh S. Cumming (Fellow 1923), Surgeon General of the United States Public Health Service, conducted a conference on April 9 at Washington for the discussion of methods and conditions of procedure in cancer research. A subcommittee consisting of Dr. Francis Carter Wood, New York; Dr. Warren H. Lewis of the Carnegie Institute; Dr. William H. Howell, Baltimore; Dr. James B. Murphy, New York, and Dr. Joseph W. Schereschewsky, Boston, was appointed to arrange a research program for early submission.

#### DELIVERED FIFTH HARVEY LECTURE

Dr. George R. Minot, F.A.C.P., Clinical Professor of Medicine of the Medical School of Harvard University delivered the fifth Harvey lecture before the New York Academy of Medicine, March 16. Dr. Minot's title was "The Treatment of Pernicious (Addison's) Anemia."

Dr. Minot was recently made Director of the Thorndike Memorial Laboratory at the Boston City Hospital, and has also been appointed Consulting Physician to the Peter Bent Brigham Hospital.

"Dr. Alfred Stengel, Philadelphia, was elected a member of the Board of Trustees of the University of Pennsylvania on March 19, in recognition of his deep interest and great service to this institution in which he is head of the Department of Medicine. In but very few instances have members of the Faculty been elected to the Board of Trustees."

"Dr. Francis X. Dercum, Philadelphia, is President of the American Philosophical Society."

"Dr. Edward B. Krumbhaar, head of the Department of Pathology at the University of Pennsylvania, was recently elected Chairman of the Section in Medical History of the Philadelphia College of Physicians."

"Dr. C. J. Wiggers, head of the department of Physiology at Western Reserve University, Cleveland, Ohio, is reported to be conducting an interesting experiment with apparatus with which motion pictures of living heart beats can be made. An attempt is being made by which life can be restored to persons whose hearts have stopped beating due to electric shock."

Dr. Ross V. Patterson (Fellow), Dean of the Jefferson Medical College of Philadelphia, conducted a Heart Clinic at the April meeting of the Eighth District Medical Society of Greensboro, N. C.

Dr. James M. Anders (Master), of Philadelphia, has been appointed by the Secretary of Commerce, Hon. Herbert Hoover, as Chairman of a Committee to conduct a Better Homes Campaign.

Dr. Frederic W. Schlutz (Fellow), Professor of Pediatrics at the University of Minnesota Medical School, addressed the April meeting of the Milwaukee Pediatric Society on "Observations on Protein Metabolism in Nephroses."

Dr. Aldred Scott Warthin, First Vice-President of the College and Editor of the *Annals* presided at the meetings of the American Association for Cancer Research and the Association of American Physicians held in Washington in association with the Congress, April 30 and May 1, 2 and 3.

At a meeting of the Board of Regents of The College at Washington, D. C. on April 29, President Charles F. Martin appointed the following Fellows members of the Board of Governors to represent their respective states until the next regular elec-

tion of Governors. Dr. Ernest E. Laubach, Boise, IDAHO; Dr. Thomas T. Holt, Wichita, KANSAS; and Dr. William M. James, Panama City (PANAMA and the CANAL ZONE).

The Board of Governors performs increasingly important functions in The College. It annually elects new members of the Board of Regents, the active governing body of The College, it recommends for election all incoming Associates, and it conducts other routine business which may be brought before it by the organization or the Board of Regents. Individual members of the Board of Governors investigate the records of all applicants from their respective states, and in various ways further the interests of The College in their localities.

Dr. B. W. Black (Fellow, 1927), resigned as Medical Director of the U. S. Veterans Bureau recently to accept an appointment as Medical Director of Alameda County, California. Dr. E. O. Crossman has succeeded Dr. Black as Medical Director of the Veterans Bureau.

Dr. Aristides Agramonte, Havana, Cuba, was among the many distinguished speakers and guests at the Twelfth Annual Clinical Session of The American College of Physicians at New Orleans. Dr. Agramonte is best known for his research in yellow fever and as a member of that distinguished group of army officers, including besides himself, Reed, Carroll, and Lazear, which was appointed by the United States to conduct its investigations in Cuba.

On March 12, during the Clinical Session, Tulane University honored Dr. Agramonte by conferring upon him the degree of Doctor of Laws, and the New Orleans Association of Commerce, at a luncheon, presented him with a life membership, engraved in gold, in recognition of the gratitude of New Orleans for his part in the investigation and control of yellow fever. Today yellow fever is practically unknown to occur in New Orleans, while preceding the appointment of the committee, and

their subsequent studies, a single epidemic of this disease caused more than four thousand deaths in New Orleans alone.

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#### *DR. ALDO CASTELLANI KNIGHTED*

Announcement has recently been made that Dr. Aldo Castellani, F.A.C.P., Professor and Director of the Department of Tropical Medicine, Tulane University of Louisiana, School of Medicine, New Orleans, has had the honor of knighthood conferred upon him in recognition of his distinguished service to the British Government for work in the field of Tropical Medicine.

Though born in Florence, Italy, Dr. Castellani spent his youth in England, and later studied in Germany. He is credited as a discoverer of the "absorption test" for the differentiation of closely allied organisms. The British Government secured Dr. Castellani's services in conducting research on sleeping sickness in Africa, 1903. Later he was appointed Director of the Institute of Bacteriology at Colombo, Ceylon, and still later became head of the clinic of tropical diseases and conducted numerous researches.

Dr. Castellani is joint author with Dr. Albert J. Chalmers of "Manual of Tropical Medicine," a widely known publication.

From 1914 to 1919, he was Professor of Tropical Medicine at the Royal University at Naples, and thereafter lecturer on Mycoses, at the London School of Tropical Medicine. During the World War, he served as Lieutenant Colonel in the medical service of the Italian Navy. In 1925, he was appointed to the chair of Professor of Tropical Medicine at Tulane.

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#### *OBITUARY*

Dr. Adam Joseph Simpson, Chester, Pennsylvania, (Fellow, April 1, 1923). Died April 6, of Heart Disease; age 49.

Dr. Simpson received his medical degree from the Gross Medical College, Denver, in 1901 and later pursued postgraduate study at the Graduate School of Medicine of the University of Pennsylvania and at the Massachusetts General Hospital. From 1904 to 1914, he was a member of the Medical Dispensary Staff of the University of Colo-

rado School of Medicine. Later he removed to Chester, Pennsylvania, where he was a member of the Medical Staff of the Chester Hospital, from 1916 until the time of his death. He was a member of his County and State Medical Societies, and a Fellow of The American Medical Association.

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With the appearance of the June number of *ANNALS OF INTERNAL MEDICINE*, Volume I will be completed. It is important that notice of renewal of subscription for a continuance of Volume II be sent promptly to the Executive Secretary, Mr. E. R. Loveland, 37th & Chestnut Streets, Philadelphia, Pa.

The Journal is occupying a high place among publications on Internal Medicine, as evidenced by its increased demand and rapidly growing circulation.

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#### *ADVERTISING IN ANNALS*

The Board of Regents and the Publication Committee of The College have expressed the wish to have advertising in *Annals of Internal Medicine* promoted among publishers of high grade medical books and manufacturers of the most reputable instruments and therapeutic products. Publishers and manufacturers have not hitherto realized the possibilities of advertising through this medium, nor have they taken into consideration the preferred class our subscribers and members represent.

The College does not seek the advertisements of any but the highest type. To this end, the following committee on advertising censorship has been appointed:

Harlow Brook, New York

Edward J. G. Beardsley, Philadelphia

George Morris Piersol, Philadelphia

All inquiries and communications concerning advertising should be sent to the Executive Secretary, Mr. E. R. Loveland, who will be aided by the above committee. Advertising rates and contract forms will be sent upon request. Members of The College are urged to co-operate in securing the advertising which will prove helpful to the journal, and aid somewhat in defraying the costs of publication.



NO NEW EDITION OF YEAR BOOK  
FOR 1928

The Board of Regents, at a meeting in April at Washington, D. C., determined to print the YEAR BOOK of The American College of Physicians only every two years. Inasmuch as the last edition was printed during the summer of 1927 and dated "1927-28," there will not be another edition before

the summer of 1929 for "1929-30." However, the Executive Secretary will prepare a suitable supplement containing all elections, changes in membership, biographical data, etc., and distribute it early in September. This supplement will be prepared in suitable form for inserting in the 1927-28 YEAR BOOK, thus giving all members a complete directory.

# Cancer and Heredity\*

MAUD SLYE, *Chicago, Illinois*

From the Otho S. A. Sprague Memorial Institute and the University of Chicago.

THERE are two aspects of this work that I wish especially to stress at this time. First I wish to show with what complete accuracy problems in the relation of heredity to disease can be worked out; second, to emphasize how great a need there is that this relation of heredity to disease should be thoroughly worked out for man, and to suggest the almost incalculable value such studies would have for the future of preventive medicine. Indeed, as I see it, they would revolutionize preventive medicine.

Almost nowhere in the field of scientific research have the findings been so entirely ignored as have been the findings regarding the relation of heredity to disease. During the past thirty years, there have appeared from various research laboratories, suggestions more or less definite that there was a relation between heredity and the occurrence of cancer in experimental animals, the tests being made for the most part with experimentally induced cancer, mainly grafted cancer.

For the past nineteen years I have been making an exhaustive study of this problem of the relation of heredity

to predisposition to cancer and exemption from cancer, with all its related problems dealing with the nature and the minutiae of behavior of malignant diseases. Mice were selected for the work for the following reasons: they are mammals and the disease problems they present closely approximate human disease problems. They are small and a sufficient number of them to furnish conclusive evidence can be maintained without an excessive budget. Also very many generations can be studied in the lifetime of one worker. Most important of all their cancers are almost identical with those of man in type, in the organs involved, and in clinical course and behavior.

The malignant growths which this stock has furnished have included practically every type and location known in human pathology and the stock has also yielded many cases of leukemia, both myelogenous and lymphatic; of pseudoleukemia and lymphosarcoma.

All conclusions have been based upon numbers so large as to be beyond all possibility of coincidence and to allow a very wide margin for possible error. The numbers involved are to date over 67,000 necropsies, including between 5,000 and 6,000 primary spontaneous neoplasms.

\*Presented before the American College of Physicians, March 5, 1928, New Orleans, La.

These cancers are not caused by any experimental procedure, as are the tar cancers, the grafted cancers, the cancers arising after infesting the animals with large numbers of parasite larvae, or any other experimental method. They are spontaneous cancers, arising in the natural life of the animals, exactly as man's spontaneous cancers arise. Thus there is no chance in the study of spontaneous tumors of involving any unconsidered quantities not present in human cancer, as may possibly be done in all experimentally induced tumors. The relation which heredity has seemed to bear to the occurrence of all of these spontaneous tumors has been consistently identical.

Searching tests have been carried out which conclusively show that cancer is not contagious in my stocks of mice. Every mouse is allowed to live out his full span of life, and to die a natural death. The clinical course of cancer is closely studied throughout the life of the animal in every case where the tumor can be diagnosed during life. Necropsy is performed as quickly as possible after death, and all suspicious tissues are microscopically examined.

*The Inheritability of the Cancer Tendency.*—The methods of studying the relation of heredity to the occurrence of spontaneous cancer in the laboratory have been the same as those which would be followed in studying intensively the inheritability of any character whatever, and the criterion of the inheritance behavior of cancer has been identical with the most rigid criterion that could be applied in any study of heredity.

In 1865 Mendel worked out with garden peas a study of the method of heredity. Later Cuenot and others working with mice, found that the mendelian method applied also in the inheritance of the animal characters tested. Throughout these studies hereditary predisposition has been shown to bear a definite relation both to the tendency to be exempt from cancer and the tendency to be susceptible to it. In thousands of mice bred in the laboratory, the tendency to be exempt from spontaneous cancer was transmitted as a simple dominant character along mendelian lines.

*Results of cross breeding.*—When a cancer-free mouse was mated with a cancerous mouse, none of the first generation offspring had cancer. The tendency to be exempt from cancer thus behaved like a simple mendelian dominant. If however, two of these first generation hybrids were mated, one-fourth of their offspring were susceptible to cancer, while three-fourths were exempt from it. Thus the tendency to be susceptible to cancer behaved like a simple mendelian recessive. If, instead of mating two first generation hybrids, each first generation hybrid was mated with a cancer-free mouse, no cancer appeared in the second generation. In this manner, that is by mating all first-generation hybrids with cancer-free mice, all cancer susceptibility has been ruled out of the entire family for many generations.

The tendency to be susceptible to cancer is also inheritable, but it is inheritable as a recessive character. This means, that even though there has been a great deal of cancer in one side of

the family, even 100%, if there is no cancer in the other side of the family, all of the immediate progeny have been cancer free. If they in their turn have been mated with cancer resistant individuals, cancer has been eliminated from their immediate families also.

By the successive mating of dominant non-cancerous mice with hybrid non-cancerous mice, cancer has been held off indefinitely but has still been present potentially, transmitted by the hybrid carrier through generation after generation, but never frankly shown as long as dominant non-cancer is mated with hybrid carriers. But when, in any generation, the 2nd, the 3rd, the nth, two hybrid non-cancerous mice have been mated, cancer has appeared in the next generation in almost mendelian ratio where the mice have lived well into cancer age. In the studies in this laboratory cancer has been held off for twenty-five generations by persistently mating analyzed dominant non-cancer with hybrid carriers through successive generations. But when eventually two of these hybrid carriers were mated, cancer has appeared in the next generation.

It is this possibility of transmitting cancer through successive generations by the right selective mating, without its frank appearance which would explain in human statistics the seemingly erratic occurrence of cancer sometimes in a family where no previous case has been known. Our human statistics however usually cover only two ancestral generations and the diagnoses in these were rarely based upon necropsy.

Out of the many hundreds of tests made in this laboratory a few typical

ones have been selected and charted here to show both the method of procedure and the kind of results obtained. Note how exactly these results follow the mendelian expectation in heredity from the given type of cross made, and how rigid is the method of analysis by which the mice are classified in regard to their cancer tendency.

In this strain the parent female was 168. She was the daughter of parents neither of which had cancer. Her mother, female 499, died in old age of chronic nephritis; and her father, male 250, died of pulmonary infection. Female 168 herself died of uncertain causes but had no tumor. She had therefore been selected for this cross as she apparently was an extracted non-tumorous mouse.

The parent male 274 died of carcinoma of the lung. He came of a family which showed at necropsy 100% of cancer (strain 139). His mother 158, died of carcinoma of the mammary gland with metastases in the lungs; his father 193, with primary carcinoma of the lung. He was therefore used in this cross because he was an analyzed extracted cancerous individual.

We have here then a typical mendelian cross between the presence and the absence of a character: that is female 168 with the cancer-resistant tendency present and male 274 with the cancer-resistant tendency absent. The first hybrid generation showed no cancer whatever, which is the typical behavior in hybridization for a mendelian recessive. *The non-cancer tendency then was dominant over the cancer tendency in this cross, just as pigmentation was dominant over the absence of*





mendelian dominant, and the cancer-susceptible tendency, like the non-pigmentation tendency, behaved like a recessive. Also, just as the type of color bred in is the one which appears in the offspring, so the types and locations of neoplasms bred in, were the ones which occurred in the offspring.

Chart 2 shows the inbred test which was given male 3904 to prove whether he was certainly an extracted pure bred cancer-resistant mouse. He was mated with his sister female 3903 (also shown in chart 1). She died of suppurative nephritis without tumor and appeared also to be an extracted pure-bred cancer-resistant mouse as did all other mice in this branch. No fraternity of this branch of strain 145 has ever shown a neoplasm either malignant or benign, although the strain still persists in the laboratory and has been in existence for over seventeen years, the original cross having been made in October, 1910. We have here then analyzed pure-bred cancer-resistant mice for hybridization testing.

To further test male 3904 as an extracted dominant non-cancerous mouse, he was hybridized with absolutely unrelated female 711 who was an analyzed non-cancerous member of strain 71 and who died in old age of an aortic rupture without tumor. No fraternity of this strain 224 ever showed a neoplasm malignant or benign, although it persisted in the laboratory for five years.

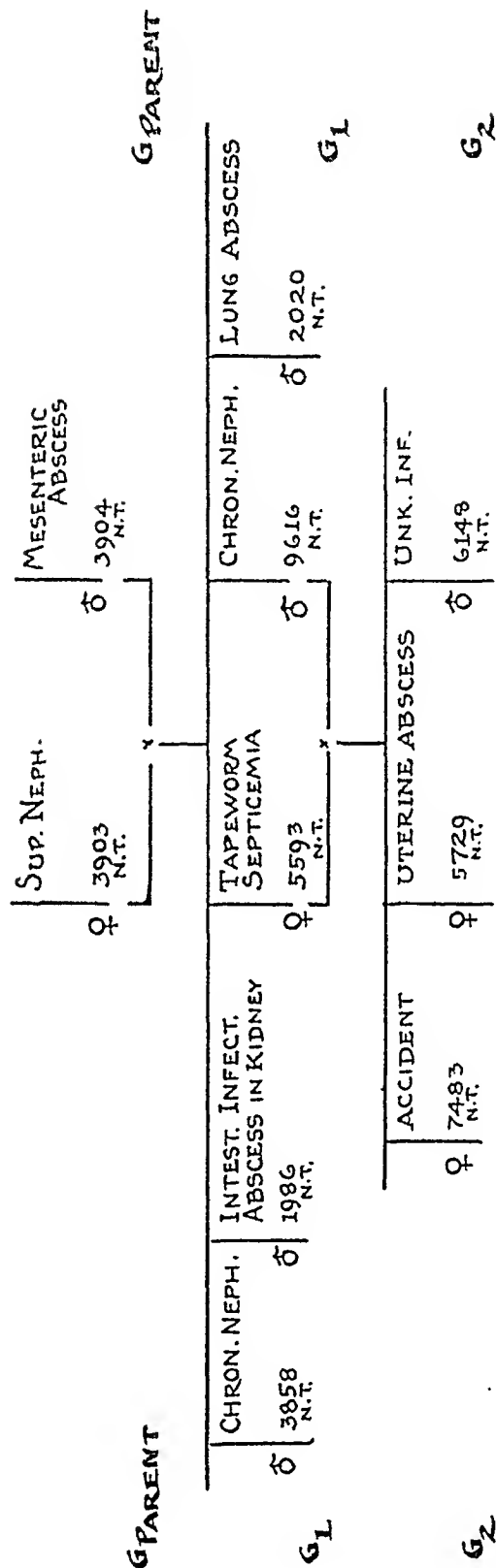
This is the method by which are analyzed all mice appearing in these studies. They are not chance mice picked up in the market or in the laboratory and mated by chance. They are analyzed individuals whose ances-

try and inheritance potentialities are known facts and they can therefore be manipulated with a certain outcome.

Chart 4 shows a part of strain 150 which resulted from the cross of analyzed cancerous female 3383 and analyzed cancer-resistant male 3904. The first hybrid generation from this cross was all non-cancerous, that is, again the non-cancer tendency was dominant over the cancer tendency; but cancer appeared in the second generation in female 9778 with a carcinoma of the mammary gland, and male 5696 with a sarcoma of the mammary gland. Again when cancerous male 5695 was mated with non-cancerous female 5786, no cancer appeared in the next generation. In both tests then shown in this chart the non-cancer tendency was dominant over the cancer tendency.

This chart shows also the origins of Branches I, II, III, and IV of this strain. Branch I is made by the crossing of two *first generation* hybrids, female 6488 and male 5426. Branch II is derived from mating two other *first generation* hybrids, female 10852 and male 8035. Branch III is made by mating two hybrid non-cancerous mice, of the *second generation* female 12148 and male 11246. Branch IV is derived by mating two *second generation* extracted dominant non-cancerous mice, female 10911 and male 11346. Note how in every case the inheritance behavior is in exact accord with the standard mendelian expectation. That is, (1) the mating of a cancerous and a dominant non-cancerous mouse gives hybrid non-cancerous mice, with cancer appearing in the second generation. (2) The mating of two hybrid non-cancerous mice gives the standard three

# PART OF STRAIN 145 INBRED ANALYSIS OF ♂ 3904 PROVING HIM NON-TUMOROUS



NO FRATERNITY IN THIS BRANCH OF THE FAMILY EVER PRODUCED A NEOPLASM  
EITHER MALIGNANT OR BENIGN.

CHART 2

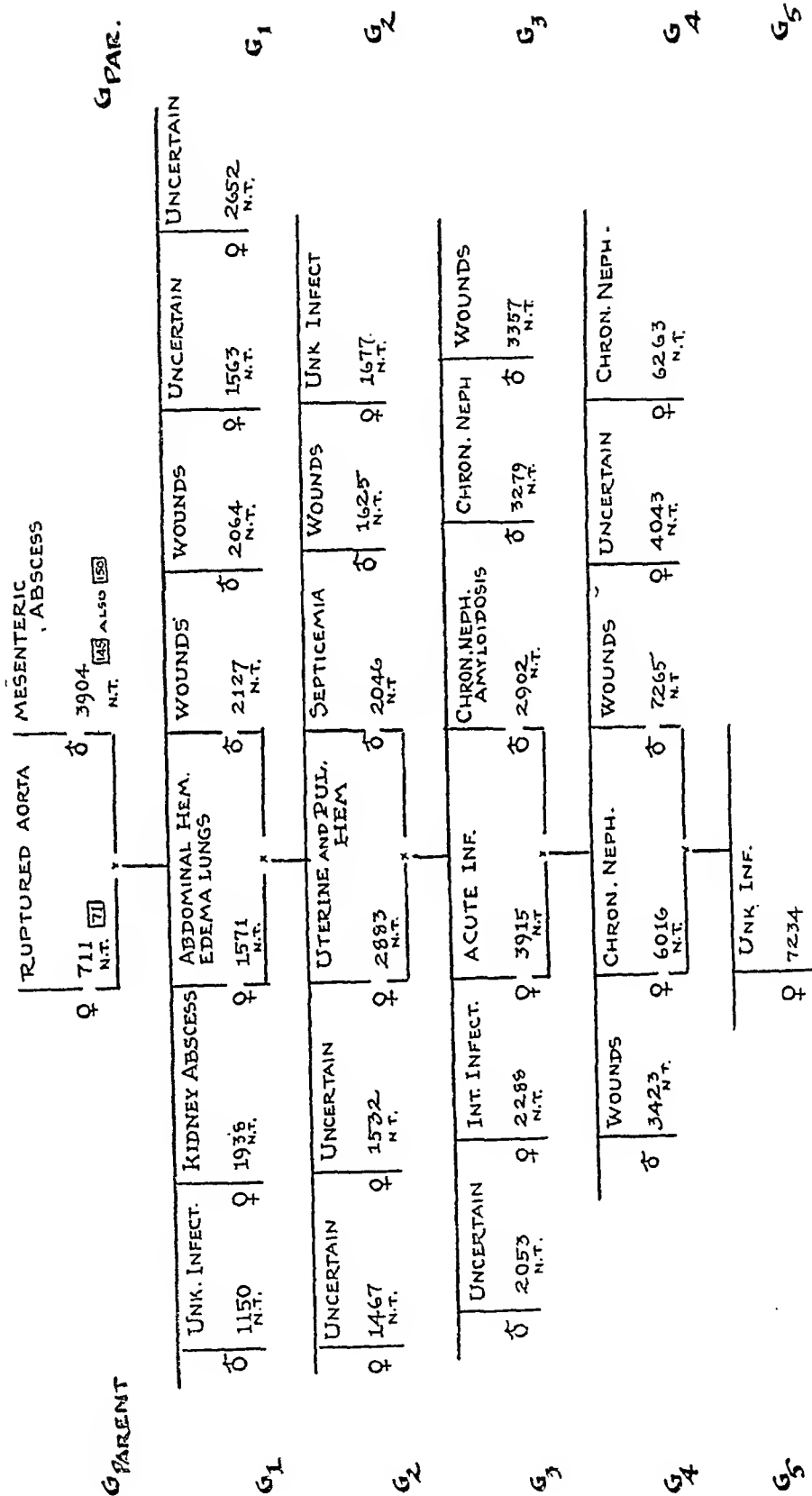


# STRAIN 224

OUTBRED ANALYSIS OF ♂ 3904 PROVING HIM NON-TUMOROUS  
 { X BETWEEN ♀ STRAIN 71 }  
 ♂ " 145 }

958

Maud Slye



NO FRATERNITY IN THIS FAMILY EVER PRODUCED A TUMOR MALIGNANT OR BENIGN.

CHART 3

PART OF STRAIN 150  
SHOWING MATING OF ANALYZED NON-TUMOROUS ♂ 3904 WITH CARCIN-  
-OMATOUS ♀ 3383

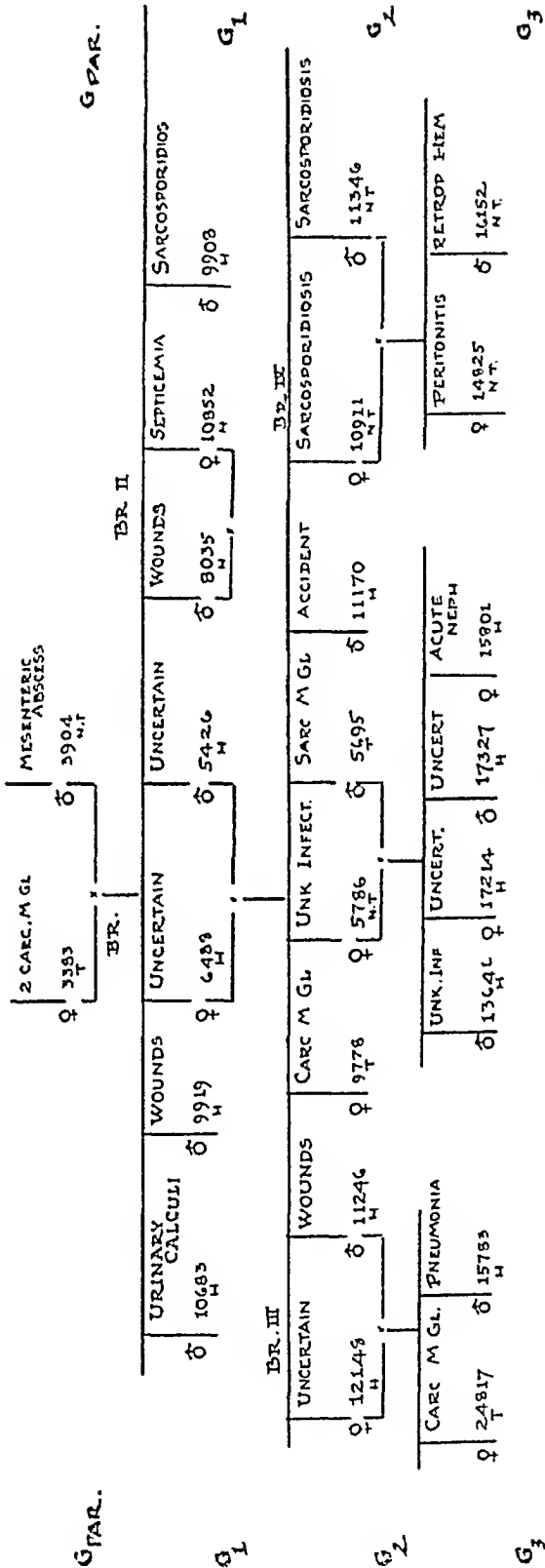


CHART 4

types, dominant non-cancer, hybrid non-cancer and recessive cancer. (3) The mating of two dominant non-cancerous mice gives extracted non-cancer only, no cancer ever appearing again in such branches.

Chart 5 gives the continuation of Branch I and shows the result of mating analyzed dominant non-tumorous female 5786 with her cancerous brother 5695 both of the second generation shown in chart 4. None of their immediate offspring ever showed tumor of any nature. Cancer thus again behaved like a recessive. Note that four branches of this family were made by mating four pairs of these hybrid non-cancerous mice, and in every case some cancer appeared in the next generation (generation 4 in the chart).

Note that throughout these charts the only tumors, both primary and secondary, which occurred, were tumors of the mammary gland and of the lung, like the ancestral tumors of the strain shown in chart I.

Chart 6 shows part of an extracted 100% cancerous strain (strain 338 Br. V) derived from double cancerous parentage, female 8619 with two carcinomas of the mammary gland and male 8751 with an adenoma of the liver. The ancestry behind this strain has been published previously. (1) It is here omitted in order to get the chart within the necessary size limits. The ancestry while in my hands, carried sarcomas, carcinomas and adenomas in most of the organs here represented.

Note the large number of liver tumors, sarcomas and adenomas, there being eleven cases of liver tumor, primary and secondary, out of twenty-four

individuals, or nearly 50%. This is very noteworthy, because outside of this laboratory there have been only two spontaneous liver tumors in mice reported in all the literature, one by the Imperial Cancer Research Laboratory of England, (2) and one from the cancer laboratory of Harvard University in Boston, Mass (3).

The liver tumors in this strain 338 were deliberately bred for, in the effort to show that the uncommon internal tumors, as well as the more common mammary gland tumors, unquestionably were determined by heredity.

In line A note female 8865 with an osteosarcoma of the mammary gland metastasizing in the liver, succeeded by her grandson male 16370 with an osteosarcoma of the subcutaneous tissues of the leg, metastasizing in the liver.

Note the very frequent occurrence in this strain of multiple tumors, particularly females 9741, 12261, 22263, 30469 and 30501. The latter two mice had more neoplastic than normal tissues at the time of their death.

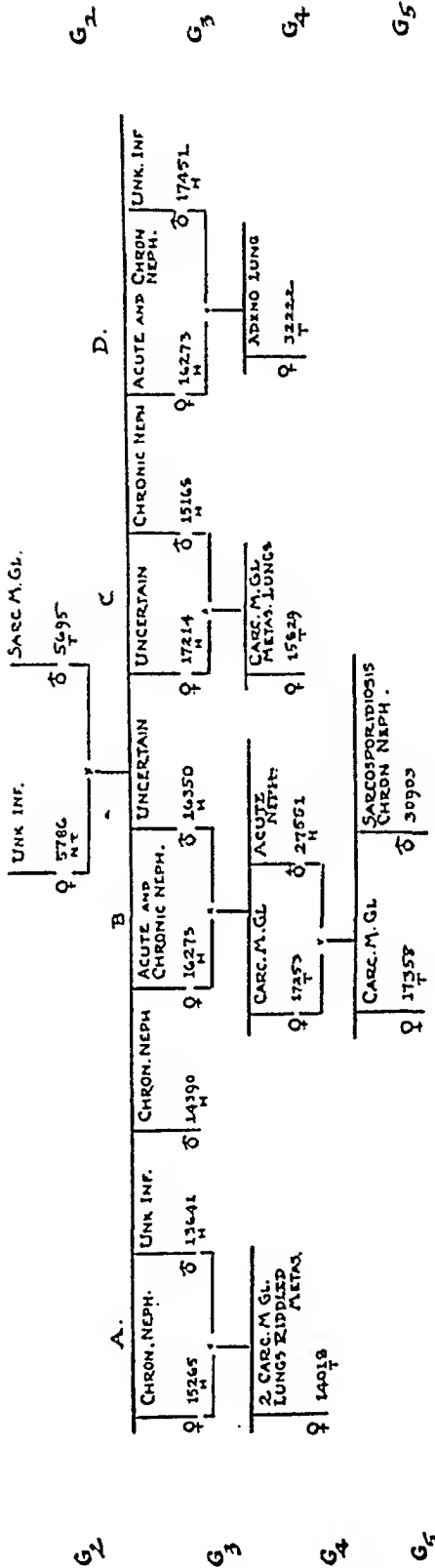
In this strain there is one case of pseudoleukemia, a disease which also occurred in the ancestry of this strain. In this laboratory chronic leukemia, pseudoleukemia, lymphosarcoma and kindred diseases have uniformly occurred in cancer strains only, and have followed the laws of heredity as surely as have neoplastic diseases. Their behavior in this laboratory would indi-

(1) SLYE: Jour. Can. Res. Vol. I. No. 4, 1916.

(2) MURRAY: Third Scientific Report of the Imperial Cancer Research Fund, 1908, 69.

(3) TYZZER: Jour. Med. Res. 1909, XXI, 479.

PART OF STRAIN 150 BR. I  
CONTINUED ANALYSIS OF MATING OF CANCEROUS WITH NON-CANCEROUS MICE



A CROSS BETWEEN A NON-TUMOROUS FEMALE AND A TUMOROUS MALE SHOWING HOW CANCER APPEARED IN THE SECOND HYBRID GENERATION FROM EVERY TESTING OF FIRST GENERATION HYBRID-CARRIERS IN LINES A·B·C·D

CHART 5

PART of STRAIN 338 BRY

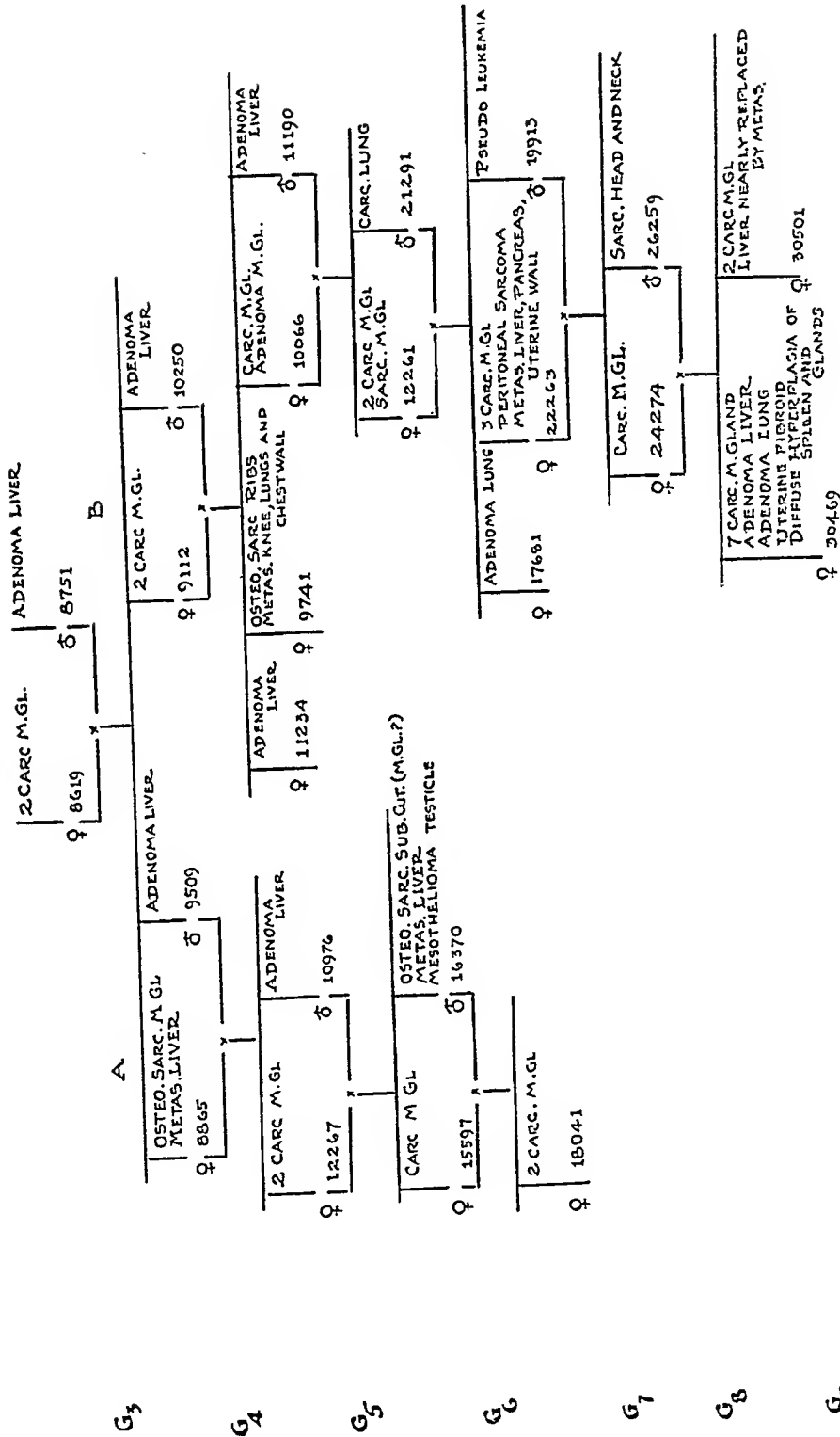


CHART 6

cate that they certainly are neoplastic diseases.

These charts are typical. Whenever in this laboratory two analyzed cancer-free mice have been mated, it has always been possible to secure 100% cancer-free families. In such crosses no instance of cancer in the succeeding strain has ever to date occurred. Also when two cancerous mice have been mated it has been possible to secure 100% cancer susceptible strains except for those mice that have died in infancy or that have been swept off by infections earlier in life than the normal age for the type of cancer to which they are predisposed. Occasionally a mouse in one of these 100% cancer strains derived from double cancerous parentage has developed a cancer when only two weeks old, although six months is an early cancer age in mice and is approximately the equivalent of about 32 years, an early cancer age in man.

In the hybridization test also susceptibility to cancer and exemption from cancer have uniformly proved to be inheritable. They have followed almost with exactness the standard expectation for a typical mendelian recessive and dominant respectively. Thus the tendency to exemption from cancer is unquestionably inheritable. Many hundreds of strains and branch strains have been carried in this laboratory, which have never shown a tumor growth of any kind. This means that in many families carried for fifty or more generations and comprising many thousands of members, there has been complete exemption from cancer. These cancer-free mice when bred into other families, carry with them ex-

emption from cancer as a dominant character. Compare this with the record of man who pays no attention to heredity in his matings, and where one in eight over a given age is dying of cancer, and note how tremendously hopeful is this fact of the inheritability of the tendency to be exempt from cancer.

Even when a recessive cancer-susceptible mouse is mated with a hybrid carrier of the cancer tendency it is possible in the third generation to derive dominant pure breeding cancer-resistant individuals. This possibility of extracting wholly cancer-free families even where one parent was cancerous and the other is a cancer carrier is a most encouraging fact and it should be strongly emphasized. From every mating of a cancer-susceptible individual with a cancer-resistant individual, either dominant or hybrid, it has been possible by the right selective mating to produce families wholly resistant to cancer.

It is this hybridization test which proves beyond dispute the inheritability of any character, for nothing but heredity could explain the segregating out and the transmission unchanged of characters in which the two parents are unlike, and the perfect mendelian pattern which they follow: as for example, albinism and pigmentation, or cancer susceptibility and cancer resistance.

Where both parents die of the same disease and all the later members of the family die of the same cause, as in a 100% inbred test, we have no absolute demonstration that it might not be a case of epidemic contagion, either extra- or intra-uterine. But we cannot explain by contagion, the perfect men-

delian pattern shown in a hybridization test. This pattern by every test that can be made, the cancer-susceptible and the cancer-resistant tendencies in mice of my stocks have uniformly followed.

*The Influence of Heredity in Determining Secondary Neoplasms.*

Not only has heredity definitely controlled the occurrence of primary tumors, but it has also controlled the occurrence of secondary tumors. (4) The tests made in this laboratory have shown that the only secondary tumors which occur in any strain, correspond with the primary tumors within that strain, both in type and in the organs in which they occur; thus showing that only those organs susceptible by heredity to primary tumors in any individual or strain, are susceptible to secondary growths.

These tests have demonstrated also that secondary tumors are as potent as primary tumors in heredity, in determining the type and the location of primary neoplasms in mice. That is, for example, the tendency to primary sarcoma of the kidney has followed from an ancestor with secondary sarcoma of the kidney, and vice versa. Note chart 7.

Strains 48 and 292. The parents in these strains are female 3 and male 360. Female 3 had a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and sarcoma metastases in the kidney. She came of a family (strain 90) which carried also tumors of the mesenteric glands, ovary, spleen, adrenal and lungs, as well as leukemia and pseudoleukemia. She

proved to be a hybrid carrier of the tendency of these organs to be susceptible to cancer, as well as of the tendency to leukemia and pseudoleukemia, and she transmitted the tendency to tumors in all of these organs to some of her posterity in hybrid crosses with analyzed dominant non-tumorous mice. She also frankly showed mammary gland, liver and kidney neoplasms of both carcinoma and sarcoma types.

Parent male 360 was the son of male 436 who died of carcinoma of the lung. This strain also carried mediastinal tumors primary and secondary. Male 360 then, was a 1st generation hybrid carrier of tumors of the lung and mediastinum, although not frankly showing tumor.

We have here then the mating of a tumorous female with a hybrid-carrier male. The first hybrid generation from this cross showed some tumorous individuals and some hybrid carriers in about equal numbers.

Note that both the primary tumors and the secondary tumors are of the same types and occur in the same organs as those bred in.

These strains were selected because they show locations of neoplasms in mice which have not been reported at all or else rarely reported from other laboratories. This chart shows that these internal tumors, difficult to diagnose clinically, follow exactly the same laws of heredity as do the easily noted mammary gland and skin tumors.

It is very difficult and laborious to secure these strains yielding high percentages of internal tumors, because it is so difficult to diagnose them before the death of the mouse and in time to secure offspring from such a selected

(4) SLYE: Jour. Can. Res. Vol. VI, No. 3, 1921.

PARTS OF STRAINS 48 AND 292

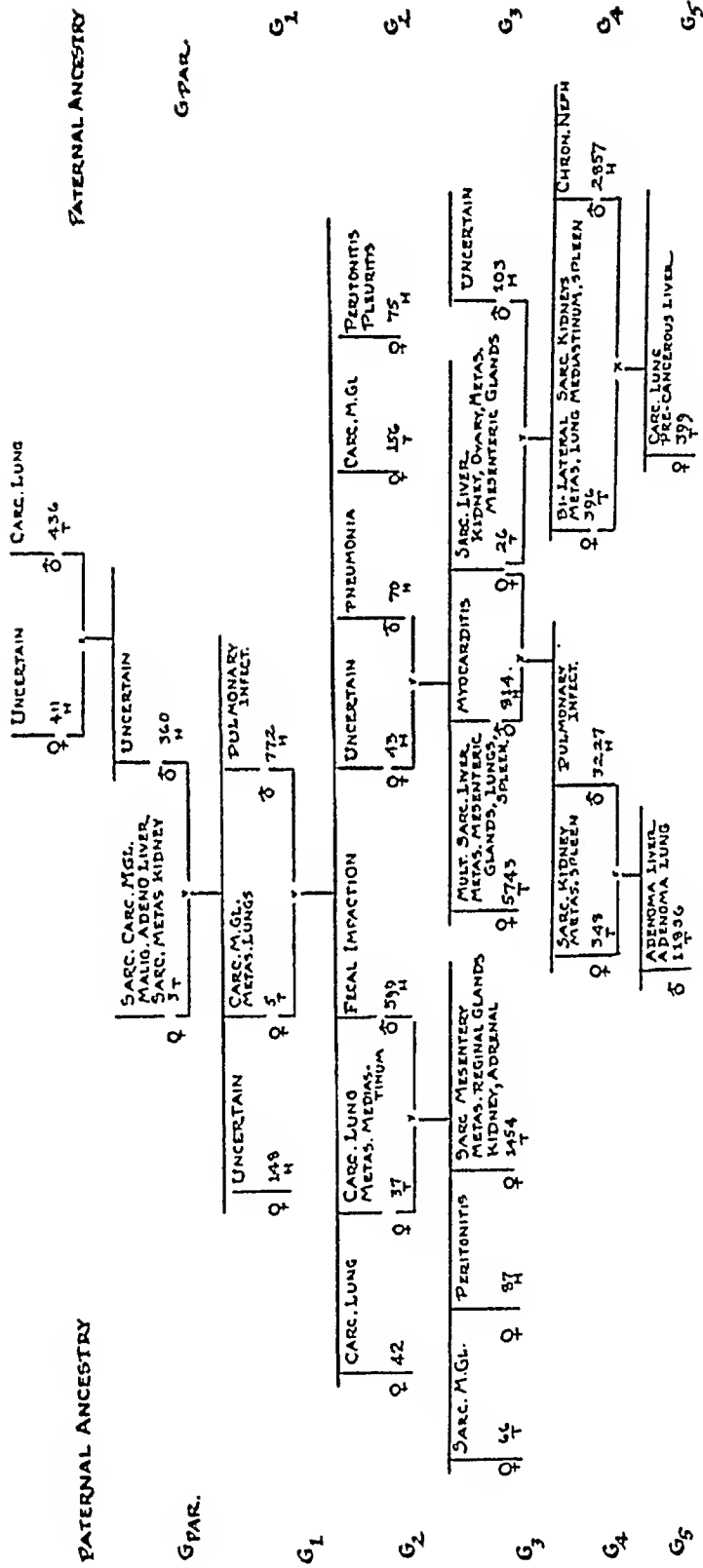


CHART 7



cancerous parentage. Only by long continued and painstaking effort is it possible to obtain them, but when we find 5 sarcomas of the kidney, 4 sarcomas of the liver, 3 sarcomas of the mesentery, 1 sarcoma of the adrenal, 3 sarcomas of the spleen, and 1 sarcoma of the ovary, in addition to numerous carcinomas of the mammary gland and lung, in a little family of sixteen members, whose ancestry was known to carry all these types of tumors, the certainty of heredity control is evident.

It has been suggested that mammary gland cancer being the most commonly reported tumor in mice, might occur by chance in these large numbers, but it is not possible to think that such rarely reported internal tumors as those shown in this typical chart, could have occurred in such numbers by chance.

Many strains in this laboratory (4) have been so manipulated in selective breeding as to exclude primary tumors of the lung, which are common tumors in mice. The lung is also one of the most frequently reported seats of secondary growths in mice. In such strains in my stocks where primary lung tumors never occur, no tumor metastases grow in the lungs even where tumor emboli are very numerous in the lung blood vessels.

Chart 8 shows a 100% lung tumor strain, strain 139. Every member of this family that lived to be six months of age or over, showed lung carcinoma either primary or secondary.

Chart 9 shows another lung tumor strain. Every member of this family

except male 2501 had lung carcinoma either primary or secondary. Male 2501 had a testicular tumor only.

Chart 10 shows a part of strain 392. Note female 12058 of the fourth generation shown in the chart. If her statistics had been taken for three generations only no tumor would have been shown in the family. But if we examine one generation farther back we find almost the duplicate of the new growths shown in female 12058. This indicates how deceptive may be the results of an examination of the death causes in the ancestry for even three generations. It also indicates how the tendency to cancer persists in hybrid carriers through generation after generation, until the right mating is made; when the cancer tendency appears in the next generation.

Charts 11 and 12 show the almost perfect inheritance behavior of thyroid malignancy as a simple mendelian recessive, occurring in strain J. D. 30-62-68. The mating is between female 24843 with thyroid carcinoma, and non-cancerous male 24383. The first hybrid generation (gen. 15 in the chart) showed no tumor. No tumor appeared in the second hybrid generation, where it might have been expected; but all of these mice died rather early for the occurrence of thyroid malignancy. When two of the 16th generation mice were mated however, thyroid malignancy occurred in the next generation. Again in generation 18, from the mating of cancerous female 31909 with non-cancerous male 32556, no cancer occurred in the next generation. But when two of these hybrid carriers were mated, thyroid carcinoma occurred in the next generation, female

(4) SLYE: Jour. Can. Res. Vol. VI, No. 2, 1921.

# STRAIN I39

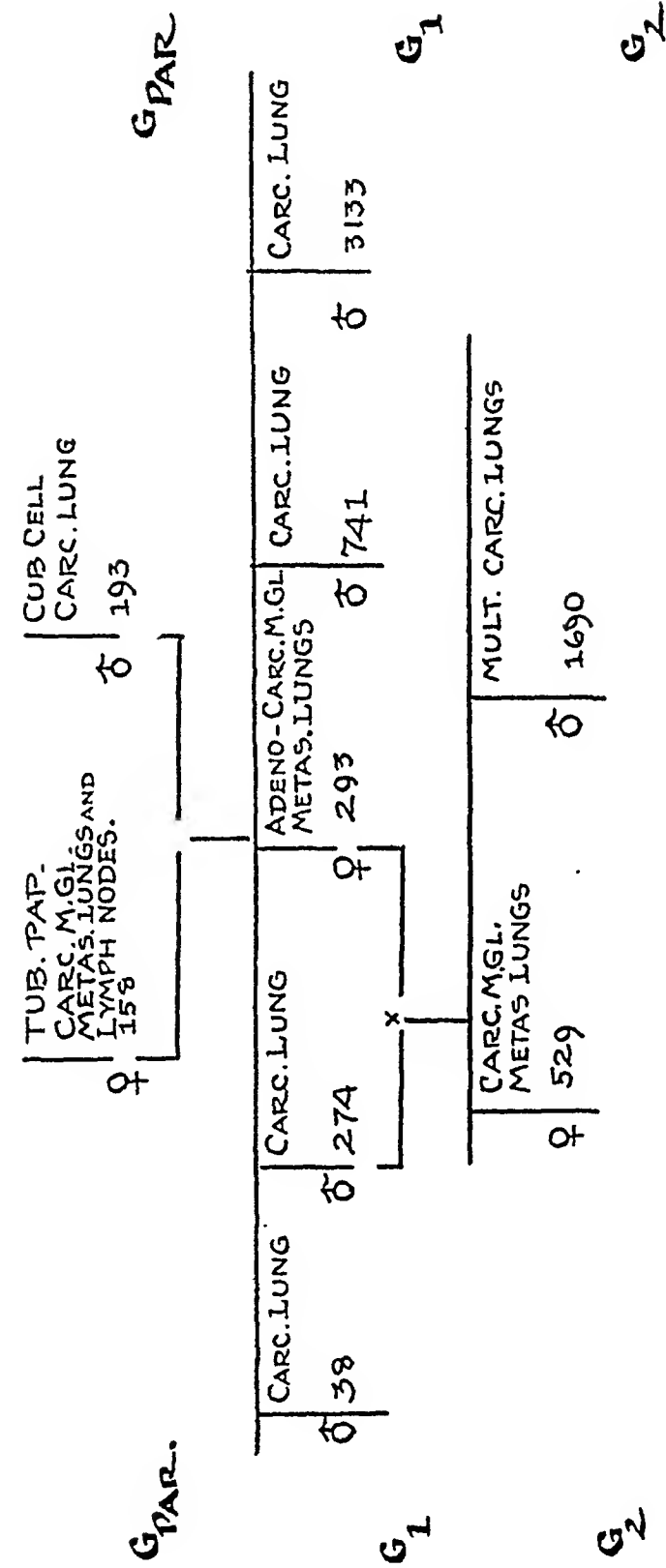
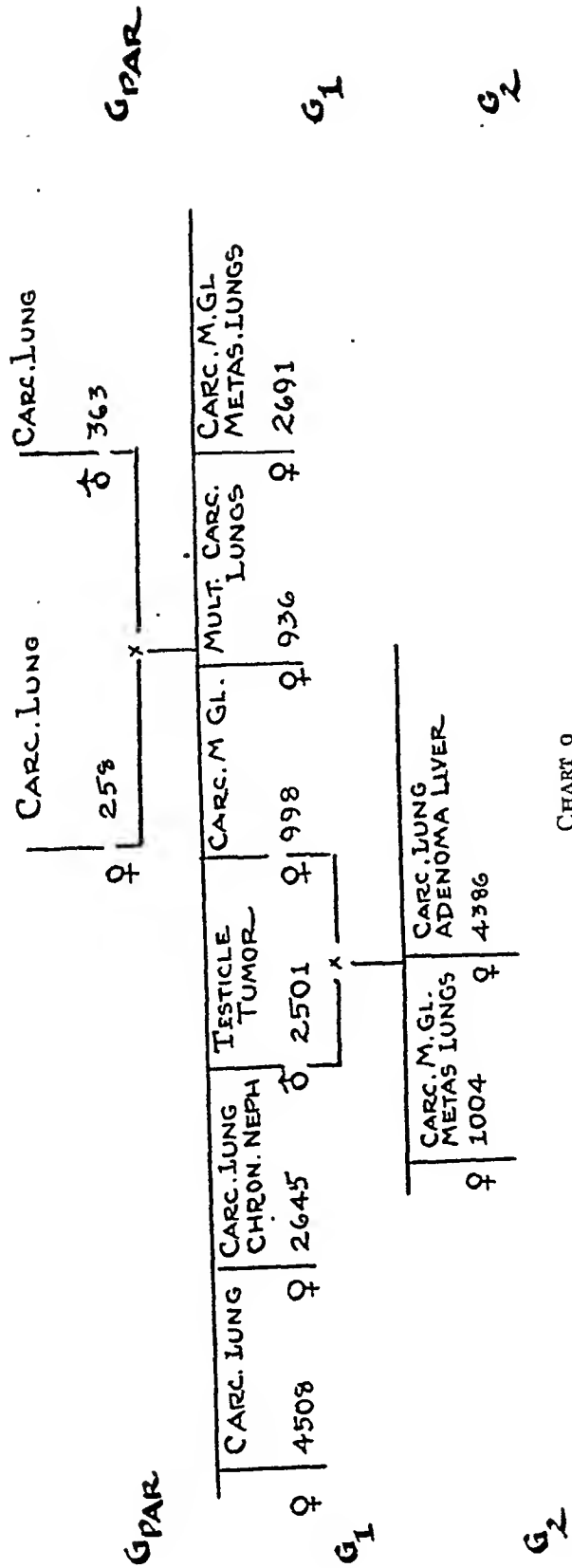


CHART 8

STRAIN 280



37841. When this female 37841 was mated with hybrid carrier male 35938, thyroid malignancy occurred in the next generation. This chart shows the almost perfect inheritance behavior of a given type and location of malig-

Chart 12 shows how by the continuous mating of a non-cancerous individual with a hybrid carrier in each successive generation of this same family after the 22nd generation, all malignancy was held off for five genera-

## PART OF STRAIN 392 ~

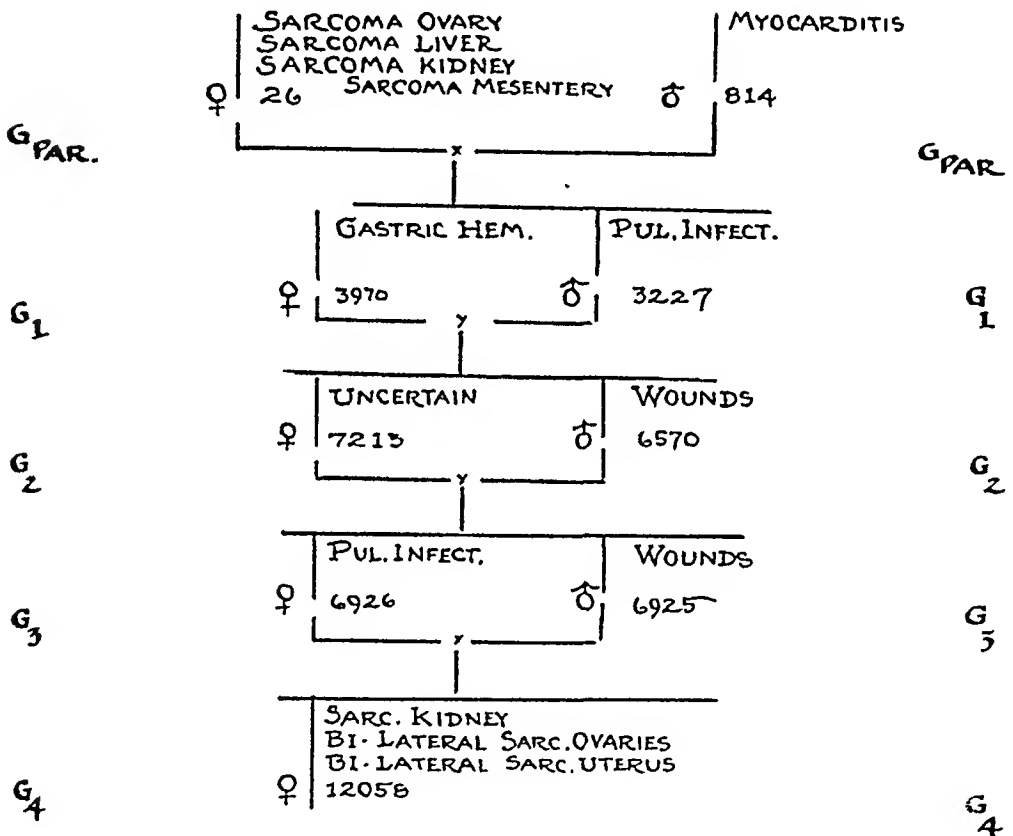


CHART 10

nancy, (that is sarcoma-carcinoma of the thyroid) as a simple mendelian recessive character. This is very striking, because thyroid malignancy in mice has nowhere else been reported. This classic occurrence of this type of tumor deliberately bred for in one family of mice, is noteworthy.

tions. The tendency however was still present in the family, transmitted by the hybrid carriers through generation after generation. When in the 27th generation two of these hybrid carriers were mated, sarcoma-carcinoma of the thyroid occurred again in the 28th generation. This is the most stringent

test that can be made to show whether or not any character has a hereditary basis. The occurrence of thyroid malignancy in the 28th generation of this family showed the perfect mendelian ratio of one-fourth cancer free, to two-fourths hybrid carrier, to one-fourth

cations. This branch of the family was chosen to show this particular type of proliferation. Other branches of the family showed malignancy in other locations, according to the matings made. In my experience, these pre-cancerous proliferations of muzzle skin and eye-

STRAIN J.D. 30-62-68 —  
GENERATION 15 — GENERATION 21

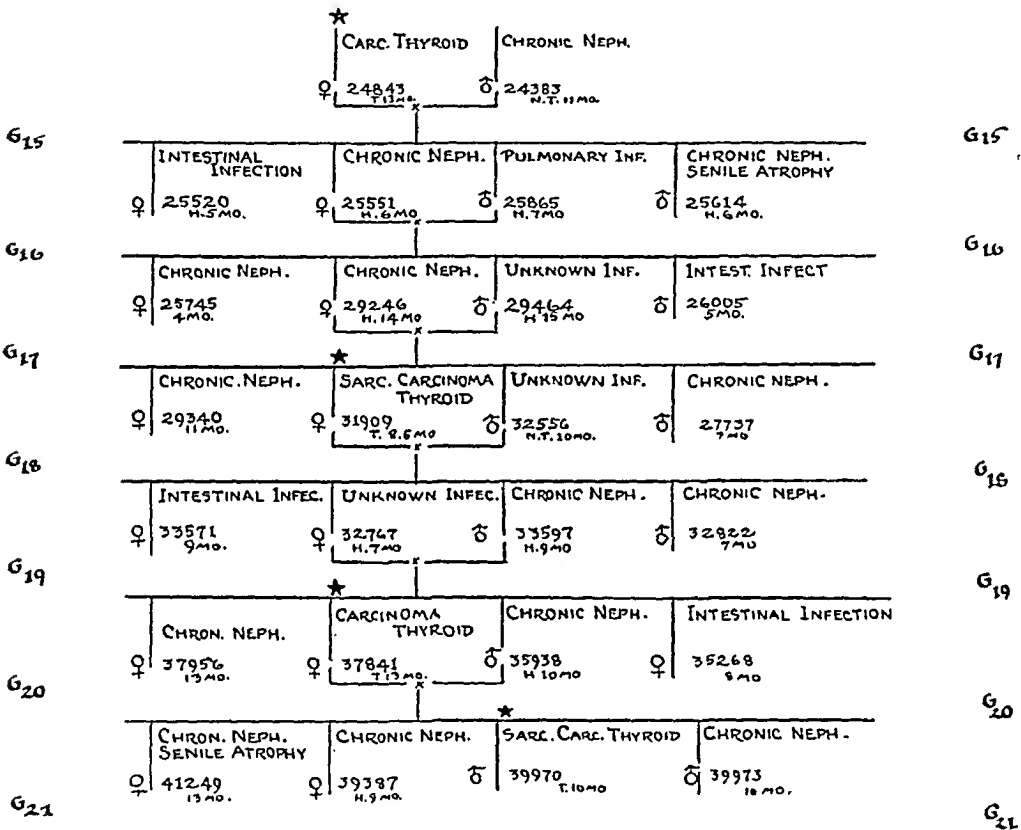


CHART II

thyroid malignancy. Some of the non-tumorous members of the family are omitted, in order to get the chart within the necessary limits.

Chart 13 shows a family of strain 150 derived from the mating of two cancerous parents. Note the high percentage of basal-cell carcinoma of the eyelids and muzzle skin and pre-cancerous proliferation in these same lo-

lids have gone on to malignancy in every case where the mouse has lived long enough for this to occur.

Chart 14 shows two branches of strain 215. Note the high percentage of carcinoma and adenoma of the lung in branch A and the high percentage of liver adenomas in branch B (each according to the matings made). The frequency of liver tumors in branch B

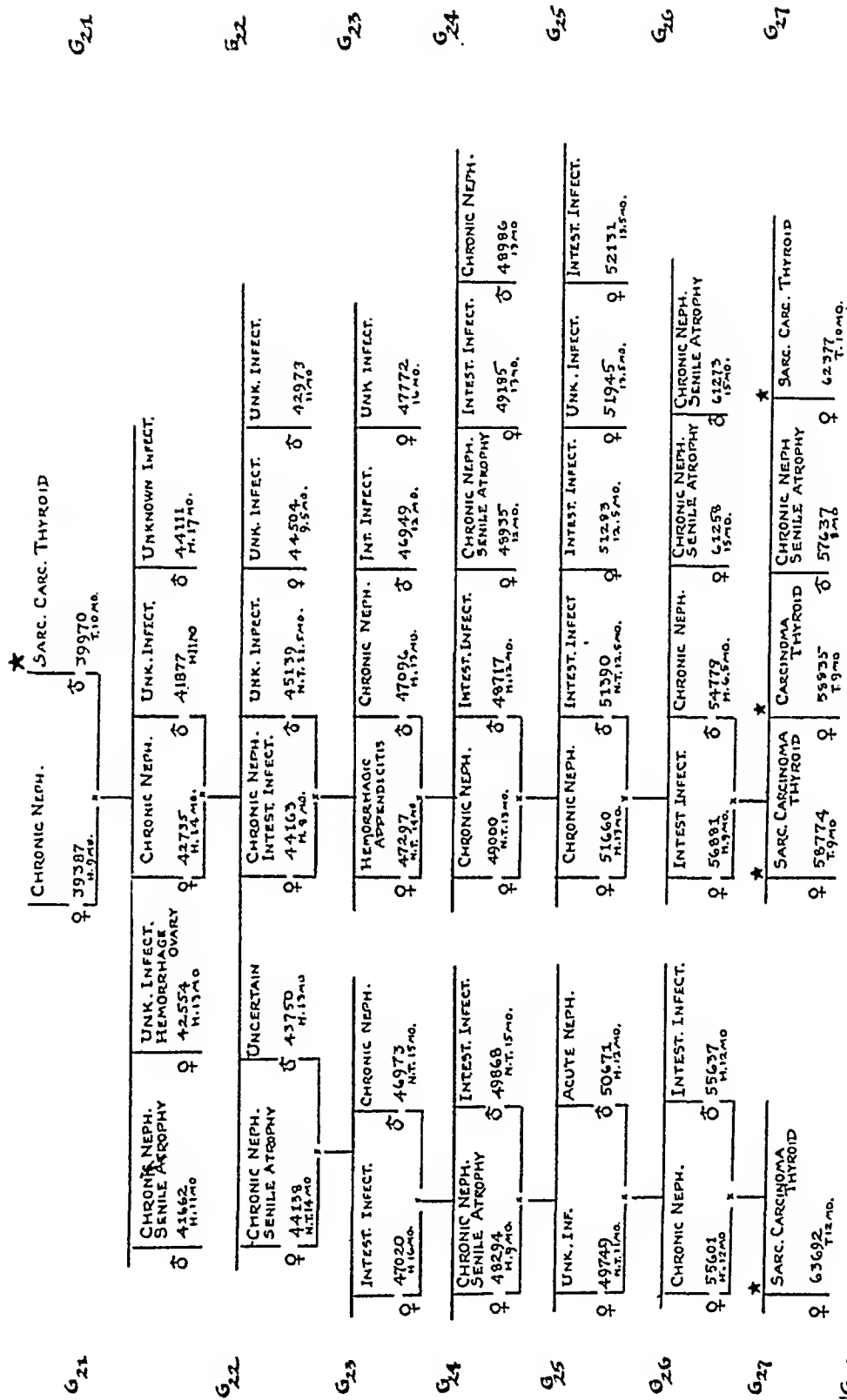
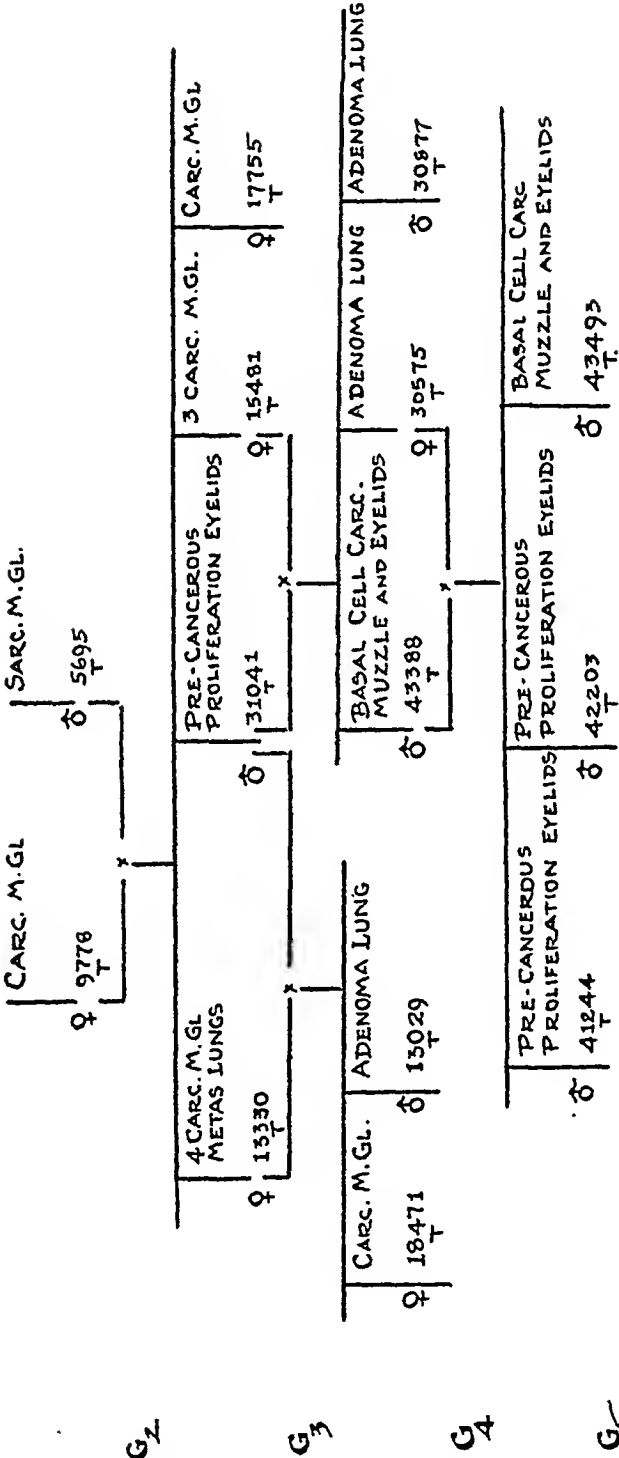
STRAIN J.D. 30-62-68  
GENERATION 21 - GENERATION 23

CHART 12

STRAIN 150 (PART 9)



A 100% TUMEROUS STRAIN FROM THE MATING OF TWO TUMEROUS PARENTS

CHART 13





is very striking as this is a tumor very rarely reported. These were malignant adenomas.

In strains which do not carry liver tumors, no secondary growths have appeared in the liver, even when multiple emboli have been present throughout the liver vessels, whereas in those strains where primary liver tumors occur, the liver is a frequent site for secondary growths, as shown in strain 338 Br. C, in strains 48 and 292.

There are apparently two factors necessary to induce cancer. If either of them could be wholly avoided, it might be possible to prevent cancer. These factors are (1) an inherited local susceptibility to the disease, and (2) irritation of the appropriate kind and the appropriate degree applied to the cancer-susceptible tissues. Experiments eliminating one or the other of these two factors, in order to see whether cancer can be avoided in this way, are being carried on in this laboratory with a promise of some success. In these experiments by avoiding either the cancer susceptible factor or the irritation factor, cancer has in some cases been avoided. The experiments thus suggest that both inherited susceptibility and local irritation are necessary in inducing cancer. They suggest that cancer susceptibility is local and not systemic. In mice susceptible to only one location of cancer, no amount of irritation or stimulation applied to other parts of the body has ever to date induced a cancer. Avoidance of irritation to the locally susceptible tissues has prevented cancer in some cases, even in susceptible individuals. This would suggest that if an individual susceptible to cancer will protect

himself against irritation of locally susceptible tissues, he might avoid cancer even though he is a member of a family with much cancer.

The fact of the inheritability of exemption from cancer is one of the few hopeful observations ever made concerning the disease, because it means that instead of every one being susceptible, large numbers are wholly exempt. It also means that it is possible wholly to eliminate cancer from any family by the right genetic procedure, as I have eliminated it from hundreds of families involving thousands of individuals.

What I have said regarding the certainty of the relation of heredity to exemption from spontaneous cancer and to the tendency to be susceptible to cancer has to do with the mice of my stocks. Its application to man and to most other animals remains to be tried. But mice are mammals like man, organ for organ their anatomy and functions are markedly similar in all fundamentals which we can test.

We find marked similarity in such types of tissue behavior, both normal and abnormal, as we are able to study in man and the lower mammals. Tissue reactions in reproduction, regeneration and all the fundamental vital processes are markedly similar. The differences in refinements and complexities attach themselves only to the less basic entities.

The spontaneous cancers in mice are also similar to those of man in every essential of structure and of behavior of which we are informed. Heredity is the most fundamental of all basic biologic facts next to the fact of the existence of life itself, and it

plays the leading rôle in evolution, keeping species and even varieties pure. Heredity applies in man and it applies in mice. Man has neoplasms and mice have similar neoplasms. The suggestion that the relation between heredity and cancer must be similar in both, surely offers itself, unless we discard evolution as the explanation of organic life as it exists today. For if evolution means anything, it must mean that down the full line from the single cell to man, similar tissues derived from ancestral tissues have responded in the same way as the ancestral tissues to the same types of stimulation. Only so could an unbroken series of organisms evolve each from the preceding. The methods and facts of heredity in man would therefore seem to be similar to the methods and facts of heredity in mice, unless there is a break in the evolutionary series between man and all other forms of life, thus isolating him from every other form of life.

Therefore since it is possible wholly to eliminate spontaneous cancer from families of mice by the appropriate genetic procedure, it might prove to be possible so to eliminate cancer from families of man. This does not mean that we can relax our vigilance against any forms of chronic irritations in any case, since we have not as yet even begun to apply the facts of heredity to the human species, and we have few adequate statistics of human heredity in relation to disease. But it does mean that we should begin to get correct scientific human statistics regarding diseases in man, based upon operation, biopsy, or necropsy in every case, and not upon opinion, so that we could

make such an application because in this procedure lies much hope.

Moreover since there is in man the beginning of a genetic sense, (that is a sense for the fitness of matings) it should be possible to educate this genetic sense. This is the great hope for humanity. The way to educate it is to make generally known the facts and operation of heredity, so that man need not be blind as to what characters he is transmitting to his posterity. If, moreover, we would uniformly permit necropsy as is the invariable rule in this laboratory, the exact facts concerning diseases in man could be obtained. If these facts were then kept in permanent record in the laboratory, in two generations by the right selective matings it might prove to be possible to begin to eliminate cancer, as I have consistently and completely eliminated it from hundreds of families of mice in the laboratory.

I am aware that the problem of founding permanent correct human cancer archives is a difficult one as every great work is difficult, but it is largely for the purpose of presenting the necessity of such a foundation and to urge this society to begin it, that I am here.

Two generations of medical men will handle at least four generations of cancer patients. If we had a sufficient number of cases on record and available for study, four generations of accurate records would almost certainly give us the necessary data in each possible type of mating, to demonstrate the relation of heredity to cancer susceptibility and cancer exemption in man, or to prove that there is no such relation.

With all the experimental evidence which is now at hand on this subject of heredity, the time obviously has come when permanently available human records are the immediate requirement. The great mass of valuable human records which exists today, is, with a few notable exceptions like those of Warthin, Broca and some others, so buried in widely scattered masses of local data as to be unavailable.

If we would begin, each in his own location, to make duplicate permanent heredity records of every suspected cancer case, with duplicate permanent slides from operation, biopsy or necropsy in every case, the solution of the problem would be at hand. These duplicates, records and slides from every location should in every case be deposited in a central permanent bureau, where they can be studied together. That central bureau I greatly desire to see located in Chicago which is a central city, so that it would be possible for me to organize the data, and to begin to analyze it, thus starting the permanent foundation. Indeed I would receive it in the beginning in my own laboratory and carry on the necessary work of organization, until the permanent location should be established.

I have brought this matter before this body, because most cancer cases in their beginnings come to you. How you handle them largely determines the

outcome. It lies within your possibility to keep track of them from the beginning to the end. It is easily within your power to begin such a foundation if it appeals to you as a necessary thing to be done, and I have therefore brought the matter first to you.

There is open to you now, in my opinion, the greatest opportunity for a tremendous advance in medical science that anywhere presents itself today, that is, the practical incorporation of the immeasurable benefits of the facts of heredity into future preventive medicine. Such an incorporation will revolutionize preventive medicine. If the time were at my disposal I would show you how.

I am here therefore to beg that a committee of your organization be appointed to consider ways and means by which permanent scientific human cancer archives can be founded. I promise you every co-operation of ideas and of service that lies within my power now and in the future. I also beg the local co-operation of every member of this great society toward this end.

For if the findings in regard to the relation of heredity to malignant diseases in mice should prove to hold for man, and every biologic fact at our disposal indicates that they would thus hold, and if we make our data available, for the first time in the history of the study of this disease, the way of the complete elimination of cancer is open.

# Some Considerations Upon the Etiologic Agent in Yellow Fever\*

By ARISTIDES AGRAMONTE, M.D. (*University of Havana, Cuba.*)

A Board of U. S. Army officers in 1900-1901 (1) discovered the manner in which mosquitoes transmit yellow fever from man to man, a theory announced and advocated by Dr. Carlos J. Finlay since 1881 (2).

The result of its investigations showed the following:

1. That soiled linen, bedding, etc. so-called "fomites" are absolutely non-infective; there is no direct contagion in yellow fever;

2. That the mosquito becomes infected only when it sucks blood from a patient during the first three days, possibly four days, of his illness;

3. That the mosquito becomes capable of transmitting the disease only after ten, possibly twelve, days of having sucked blood as above stated;

4. That once infected, the mosquito is capable of transmitting the disease throughout its life-time.

These findings have been corroborated by several Committees appointed for the purpose in Cuba, Brazil and Mexico.

\*Presented before the American College of Physicians, March 5, 1928, New Orleans, La.

In taking into account the considerations that I am about to submit, it is important that we bear in mind the above facts, none of which can be any longer discussed; they have become almost axiomatic as far as the relations of yellow fever with mosquitoes or with "fomites" is concerned.

Now, in the course of the last half century, several yellow fever parasites have cropped up as the result of more or less (more often less) painstaking efforts on the part of enthusiastic investigators.

Of all these various germs, the *Bacillus icteroides* of Sanarelli (3) and the *Leptospira icteroides* of Noguchi, (4) enjoyed the greater period of credit. *Bacillus icteroides* has been discarded as having any relation with yellow fever since the Spanish-American War. Noguchi's *Leptospira* is of more recent origin and has been kept before the scientific world as the etiologic agent for the last eight years.

A cursory examination of Dr. Noguchi's claims reveals the following:

1. That *Leptospira* was obtained originally by injecting guinea-pigs with blood from yellow fever patients, the organism appearing then in the animals' blood, causing symptoms and le-

sions declared to be similar to those of yellow fever in man;

2. That the *Leptospira* infects guinea-pigs by contact and by injection into their tissues;

3. Young dogs become infected by feeding upon the *Leptospira*;

4. The *Leptospira* shows positive Pfeiffer reaction with yellow fever convalescent serum in about 90% of the tests;

5. Inoculation of animals by mosquitoes has given positive result in rare cases;

6. A vaccine and a serum have been prepared from this organism and injected as a prophylactic and a cure of yellow fever, respectively.

Several years' experience with yellow fever in the midst of severe epidemics and the fact of my connection with the work of the Army Board above referred to, induced me, from the very first articles of Dr. Noguchi to look upon his claims of specificity for the *Leptospira*, with much reticence, and a certain degree of incredulity; Noguchi's name constituted a trade-mark, (if you will allow the term), that offered unusual guarantee of excellent and thorough scientific research, just as Sanarelli's name did, in the case of his *Bacillus icteroides*.

Drs. Guiteras and Lebredo, well versed in the problems of yellow fever, both agreed with me in that some of the characteristics of the *Leptospira* did not conform with what must necessarily be characteristic of the yellow fever parasite, but still we awaited the

further conclusive experimentation that was to be expected.

In the meantime, a culture of *L. icteroides* was graciously furnished by Dr. Noguchi to my colleague Dr. Lebredo, which after repeated plantings and inoculations upon various animals in various ways, (by mouth, subcutaneously, intraperitoneally and by contact), served to further convince us that such an almost saprophytic organism could not be the elusive yellow fever parasite. (5) The cultural characteristics and the resultant lesions seemed to us not unlike those of *Lepiospira icterohemorrhagiae* of Weil's disease.

Among the peculiar characters of *L. icteroides* that do not seem to correlate with what we know of the yellow fever infection are, in the first place, the large amount of yellow fever blood necessary to inject into guinea-pigs in order to, sometimes, infect them, (2 to 5 c.c.) when we know that in the same manner, one c.c. of blood taken in the first three days of the disease, regularly produces an infection in man; further, only a minute drop, all that a mosquito needs, in due time will cause numerous cases through its sting, upon non-immunes; by the fact that in Weil's disease, *L. icterohemorrhagiae* is best obtained by injecting a large quantity of the patient's blood into guinea-pigs, even as late as the 8th or 9th day of the disease, while in yellow fever the germ is not present in the blood after the 3rd or 4th day. Another peculiarity is the fact that *L. icteroides* seems to be infective upon the lower animals in every way rather than through the mosquito, when we know by experiment and experience

that yellow fever is not transmissible, in nature, by any other way than through the mosquito. With the leptospira we have at least one instance of natural infection by mouth, of a dog, when neither ticks, fleas, mosquitoes or other insects, many of them present, carried the infection to other puppies in the same litter; the mother obtained the infection through licking her pups, two of which had been experimentally inoculated with *L. icteroides* (5).

If I may be allowed to quote from my own writing, at the International Conference held in Kingston, Jamaica, in the summer of 1924, in a paper that I had the honor to present upon "Yellow Fever Prophylaxis," (6) I said: "the serologic difference between *L. icteroides* and *L. icterohemorrhagiae* are not pronounced; in fact they are no greater than those we find between organisms that form part of a single group, etc."

This question has been definitely settled by the remarkable work of Sellards and Theiler (7), where they showed that an absolute interrelation exists, the serum of *L. icterohemorrhagiae* causing positive Pfeiffer reaction upon *L. icteroides* and vice versa, the culture of *icteroides* having been furnished by Dr. Noguchi and properly tested before using. Sellards says further (8):

"In our own laboratory Dr. Theiler and myself, (1926) carried out some cross immunity tests in guinea-pigs which were actively immunized against *L. icterohemorrhagiae* and *L. icteroides*. Under the conditions of our experiments we found no differences between the two leptospira."

Other investigators in Africa, (9)

(Gray, Connal, Aitken, Smith, 1926) obtained negative Pfeiffer reaction upon *L. icteroides*, using yellow fever convalescent serum.

The same result was obtained, (Sellards) (10) with the yellow fever convalescent serum at Parahyba, Brazil, which serum gave no protection against either *L. icteroides* or *L. icterohemorrhagiae*.

I think that evidence ought to be sufficient to set aside the claimed specific serologic tests of *L. icteroides* with regard to yellow fever.

If my contention is just and correct, and such I believe it honestly to be, what incalculable harm has not been done by appearing to protect against yellow fever by administering a vaccine prepared from an organism that has no connection whatever with the disease! I do not refer to the numerous abscesses produced, as testified to by Dr. H. R. Carter in speaking of the epidemic in Peru, when this method was practiced; no, I have reference to the false sense of security thus imparted to those who believed in the prophylactic virtues of the Noguchi vaccine. Before using it upon the population I think it should have been subjected to the test we applied in Havana to the Caldas-Bellinzaghi serum (11); surely it would have followed upon the same road into oblivion. The same may be said in all respects regarding the so-called curative serum.

But let us see for a moment how *L. icteroides* behaves with regard to the mosquito, the only route that we know by which the yellow fever germ must penetrate and leave the tissues of man.

In my paper read at Kingston, I say (6):

"When a mosquito infected from an inoculated animal, (infected with *L. icteroides*), is, twelve days afterwards, made to bite a non-immune individual causing thereby an undisputed case of yellow fever, then will be time to accept the specific character that is now attributed to Prof. Noguchi's germ. But so long as experiments and tests are restricted to the lower animals, trying to determine there-from the value of the so-called vaccine and sera in yellow fever prophylaxis, *L. icteroides* can have but a laboratory interest."

Noguchi has never reported any experiments with man; I have reason to believe he has undertaken none whatever. It was our intention to try to infect non-immune volunteers with mosquitoes fed on inoculated guinea-pigs, but the culture of *L. icteroides* at our disposal became infected and died before we were ready to attempt the experiments and I have been unable to secure another one for the purpose. If, however, as I believe from the incontrovertible facts presented, *L. icteroides* and *L. icterohemorrhagiae* are the same, no infection would result, for mosquitoes charged by biting guinea-pigs with their blood teeming with *L. icterohemorrhagiae*, after twelve days cannot reproduce the infection upon either guinea-pigs or man.

Noguchi tries to explain the twelve days extrinsic incubation in the mosquito by alleging that the leptospira requires that length of time in order to multiply sufficiently so that the insect can return it into another individual (12). The facts, however, show that as time passes after the mosquito has

sucked leptospira blood, this organism gradually diminishes in number in the stomach and intestines of the insect, proving that the latter is not a proper medium for its multiplication. Such being the case, it is logical to suppose that the longer period that transpires after sucking the infected blood, the less chances there are of its producing an infection, exactly the opposite of what occurs when the mosquito injects the real yellow fever virus.

Recent experiments with *L. icteroides* have demonstrated the correctness of the above surmises, Gay and Sellards (13) have applied mosquitoes, (*Aedes aegypti*), infected by sucking the blood of guinea-pigs inoculated with *L. icteroides* to non-immune volunteers, obtaining absolutely negative results, after the following manner:

Volunteer A, bit by 36 mosquitoes (Lot 5) 18 days after injection of *L. i.*

Volunteer B, bit by 27 mosquitoes (Lot 5) 25 days after injection of *L. i.*

Volunteer C, bit by 24 mosquitoes (Lot 6) 44 days after injection of *L. i.*

If they had sucked the yellow fever germ instead, any one of those mosquitoes would have produced a case of yellow fever. This was the experiment which I recommended should be undertaken, four years ago.

The serum of those volunteers was not protective to guinea-pigs infected with *L. icteroides*.

The same authors report negative transmission attempts with mosquitoes from infected to healthy guinea-pigs; also, that macerated infected mosquitoes when injected into guinea-pigs soon after their infection will produce the death of the animals, but if some time is allowed to elapse, no infection

of the guinea-pigs could be produced, nor were they protected, because on direct injection of leptospira, they promptly died of the infection (13).

Noguchi ingeniously but very illogically explains why the yellow fever parasite disappears from the peripheral circulation, on the grounds that in a certain culture medium prepared by him, the *L. icteroides* soon leaves the liquid portion and fixes itself upon the semi-solid part. He says (12): "I have often wondered if this peculiar habit of the *L. icteroides* will not explain why they abandon the blood after the first days of the disease rapidly invading the liver and kidneys." He forgets the fact that *L. icteroides* multiplies unceasingly and is mostly in evidence in the blood, as time passes after the inoculation of all susceptible animals, regardless of manner of infection.

In conclusion, I may say:

1. That the causative agent of yellow fever has not been demonstrated as yet.

2. That the claims of Dr. H. Noguchi and his disciples for *L. icteroides* as the specific germ of yellow fever have been conclusively disproved:—

(a) Because *L. icteroides* and *L. icterohemorrhagiae* show crossed serologic reactions indicating their identity;

(b) Because yellow fever convalescent serum does not protect against *L. icteroides* while serum from convalescents of Weil's disease does protect both, against *L. icteroides* and *L. icterohemorrhagiae*;

(c) Because *L. icteroides* gradually increases in numbers in the blood of inoculated animals, while the real yellow fever germ disappears from the circulating blood at the third or fourth day;

(d) Because *L. icteroides* fails to infect mosquitoes so that in due time the latter may infect man;

(e) Because *L. icteroides* is able to penetrate the unbroken skin and produce infection, while yellow fever has been shown to be non-contagious, even through cuts or abrasions of the skin;

3. That any vaccine or serum prepared with the *L. icteroides* can be of no value either protective or curative as regards yellow fever.

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# The Treatment of Pernicious Anemia with a Liver Extract\*†

BY CYRUS C. STURGIS, M.D., RAPHAEL ISAACS, M.D., MILLARD SMITH, M.D.,  
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THE discovery by Minot and Murphy (1) (2) that the feeding of one-half pound of mammalian liver daily to patients with uncomplicated pernicious anemia, will cause the red blood count to return to normal limits within six to eight weeks, has received repeated confirmation by numerous investigators. (3) Coincident with the changes in the blood, there is a striking improvement in the patient's general condition and strength. In general, it may be said that all of the symptoms which are directly due to the anemia itself, disappear within approximately two months after the liver treatment is instituted. Having demonstrated that liver contains some constituent which exerts this beneficial effect in pernicious anemia, the most obvious and logical problem which presents itself, is the isolation of the substance to which this property of liver is due. The most essential reasons why this active principle should be isolated are as follows:

1. If a substance can be detected

\*From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan.

†Presented before the American College of Physicians, March 6, 1928, New Orleans, La.

which controls the regeneration of blood in pernicious anemia, this may give additional information bearing on the normal maturation of the red blood cells, which in turn may lead to the discovery of useful information in relation to the more efficient treatment of other types of anemia.

2. From the standpoint of practical therapy the isolation of the concentrated active principle is of great importance. Should the substance prove to be comparatively simple in chemical structure and readily synthesized, an unlimited supply would be assured for the use of patients of limited means who have pernicious anemia. Furthermore, the active principle probably represents such a small fraction of the total liver substance that medication might be simplified to such an extent that the administration of three or four capsules daily would suffice. To maintain the red blood count in pernicious anemia at a normal level, it is necessary for the patients to continue the ingestion of a certain amount of liver or liver extract at regular intervals. The exact quantity which is necessary for the purpose is not definitely known at present. It has been our experience that all patients are unable to consume

as much as one-half pound of liver daily for an indefinite period, as some develop an aversion for it which obliges them to discontinue this form of therapy. Such patients do not object to liver in the form of a concentrated extract which can be administered in a half a glass of water or other liquids. An additional advantage of a concentrated extract is that it can be taken between meals and the patients are free, therefore, to consume foods of their own choice at regular meal hours. Moreover, some patients have complained that an adequate supply of calf's liver is not always available and furthermore, under various circumstances, such as traveling, it is not always possible to obtain the necessary amount of liver daily. The preparation of a concentrated and potent liver extract is of the utmost practical importance, therefore, to the successful treatment of the disease.

The method of preparing such an extract was reported by Cohn, Minot and their collaborators in the spring of 1927 (4) and through the courtesy of these investigators and the Harvard Pernicious Anemia Committee,\* we were permitted to give this substance an extensive clinical trial before it was released for widespread use. The extract is prepared in a manner similar to the method shown in chart I which involves treating the raw minced liver first with alkali, then acid, in order to remove the liver proteins. The coagulable blood proteins are then removed by heating to 70 degrees C. Ad-

\*The extract was prepared by Eli Lilly & Company, Indianapolis, Indiana, under the supervision of this Committee.

ditional steps are extracting the remaining solution with ether and then alcohol. The alcohol-ether insoluble residue contains the active principle. The substance thus prepared is a yellowish, granular powder, which represents approximately 1% of the whole liver. It has a slightly disagreeable, characteristic taste and is soluble in water but insoluble in ether and alcohol. According to Minot (5), it is of a non-protein nature and is free of all carbohydrate and lipoids. The earliest reports of its composition stated that traces of iron and sulphur were present but more recent statements (5) indicate that the iron may be removed without effecting the potency of the substance. Minot believes that the beneficial effect produced by this preparation is not due to any known vitamins but suggests that the active constituent is a polypeptid or nitrogenous base (5). West (6) has reported improvement in five consecutive patients with pernicious anemia, all of whom received an alcohol-ether soluble fraction of fresh beef liver. This substance studied by West, therefore, differs from the Minot-Cohn extract in its characteristics as the latter is insoluble in ether and alcohol.

#### THE EFFECT OF LIVER EXTRACT ON THE GENERAL CONDITION OF THE PATIENT.

The effect of this substance when used in the treatment of twenty-eight patients with pernicious anemia forms the basis of this report. The powdered extract made from one pound of raw liver was given once daily, but in a few instances the daily dosage was increased to the equivalent of 1½ pounds. After experimenting with many different vehicles, it was observed

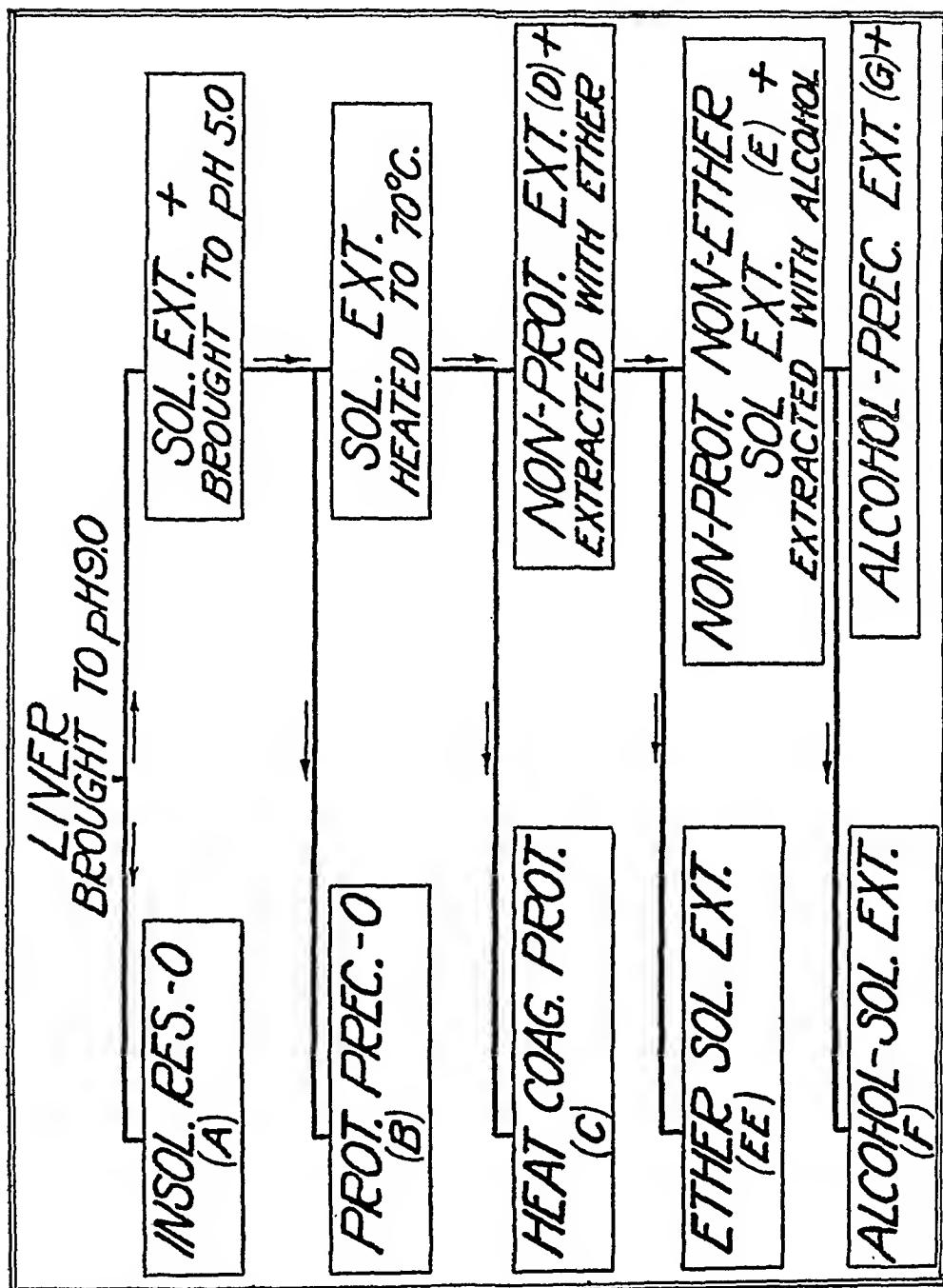


CHART I.—The preparation of liver extract according to the method of Colin and associates. The capital letters in brackets designate the fraction; + indicates that the fraction contains the active principle, O that it is inactive.

that the slightly disagreeable taste could best be masked by dissolving the powder in tomato juice or tomato bouillon immediately before it was taken by the patient. As much as the equivalent of  $1\frac{1}{2}$  pound of liver can be dissolved in one-half glass of water. The effect of the liver extract is entirely similar to that observed following the administration of an equivalent amount of cooked or raw liver. The earliest sign of improvement is usually an increase in the patient's appetite which is noted within three to five days after the treatment is instituted. Coincident with this is a disappearance of nausea, vomiting and other gastrointestinal complaints. If diarrhoea has been present it usually disappears following a few days of treatment. A few patients, however, who have not had this complaint previously, have developed a mild and transient diarrhoea after liver extract had been given for several days; the same dosage was continued and the condition disappeared without additional treatment. The fever and associated tachycardia which are observed frequently in pernicious anemia during a relapse usually subside rapidly. The patient soon gains strength and all of the symptoms which are directly related to the anemia disappear within six to eight weeks. Unless some complication exists, such as advanced changes in the spinal cord, the patient is able to resume a normal existence.

Tingling sensations in the fingers and toes remain unchanged, although some patients, because of their improved subjective condition, do not notice it as much as when they were sick, while others, being relieved of other

symptoms, have their attention directed more fully to it. The change in color of the skin is noteworthy. Frequently on the third or fourth day, and occasionally during the first or second week, the skin of the chin, tip of the nose and later the cheeks begins to flush and appear red, forming an odd contrast to the pale and often icteric appearance of the surrounding areas. Following this the pads of the fingers and later the palmar prominences likewise appear red. As this change is localized and is noted frequently before there is a significant increase in the red blood count, it is probably vasomotor in nature. After the third week, and occasionally earlier, the last sub-icteric traces leave the skin and sclera. With the progress in the improvement of the general condition the stools, which frequently had an extremely foul odor during a relapse, became more normal in odor as well as in general appearance. In those patients in whom the gastric physiology was studied after the onset of the remission, there was no return of free hydrochloric acid in the stomach contents. After the administration of the liver extract, many of the symptoms which had previously been considered as associated with an achlorhydria (belching, feeling of fullness, epigastric distress, anorexia, nausea) were no longer noted. These observations offer material for revision of some of our concepts of the physiology of gastric digestion.

#### CHANGES IN THE BLOOD FOLLOWING THE TREATMENT WITH LIVER EXTRACT AND LIVER.

The effect of treatment with the liver extract on the blood in twenty-eight

patients with pernicious anemia is shown in Table I. It is to be noted that all of the patients before treatment had a low red blood count and in the red cell count had been observed. The effect of the administration of one-half pound of cooked or raw liver to a number of patients for

TABLE I.

Patient	Initial erythrocyte count	Final erythrocyte count after liver extract therapy	Number of days of liver extract therapy	Erythrocyte count after additional days of liver therapy	Number of additional days of liver therapy
	Million cells per cu. mm.	Million cells per cu. mm.		Million cells per cu. mm.	
Ki	.50	3.10	21	5.00	82
Ry	.63	3.80	42		
Ba	.80	3.80	23	5.80	33
Or	.80	4.10	47	4.90	25
Be	1.00	3.80	34		
Gc	1.10	5.20	46	5.40	49
Ov	1.20	3.50	15	5.30	31
Wi	1.20	2.60	24	5.00	51
Cr	1.20	4.70	60		
Hu	1.30	3.10	12	4.80	58
Sm	1.30	3.60	29	4.60	56
McC	1.40	4.00	24	5.10	35
Bau	1.50	2.70	24	4.20	77
Sc	1.50	4.10	24	5.40	25
Ca	1.70	5.00	44		
De	1.80	3.70	26	5.70	91
Jo	1.80	4.50	40	5.70	16
Wr	1.90	3.90	19	5.00	24
Cl	2.00	4.60	14	5.20	44
Zi	2.10	4.00	44	5.60	17
Si	2.20	2.50	7	5.40	86
McK	2.30	3.60	30	4.80	56
Os	2.30	3.30	19	4.50	31
Ro	2.30	5.00	33	5.30	31
Gi	2.30	4.20	21	5.30	29
			26		
Va	3.60	4.50	14		
Mo	3.80	4.60	15		

in each instance there was a very striking increase following the use of liver extract. In a number of patients the use of liver extract was discontinued and the patients given one-half pound of liver daily after a convincing rise

a variable period of days is shown, therefore, in addition to the results obtained by the use of the liver extract. From observation of this series of patients it seems reasonable to deduce that in those with uncomplicated pernicious

ous anemia the red cell count can be increased to normal by means of a liver extract, prepared according to the method devised by Cohn and Minot.

As Murphy, Monroe and Fitz (7) have emphasized, the earliest response to the feeding of liver is an increase in the number of reticulocytes of the peripheral blood which is usually apparent a week or more before the rise in the total red blood count can be demonstrated.\* This increase is rarely absent in patients who have a low red blood count. It is observed within three to six days after the treatment is begun and usually reaches its height on the seventh or eighth day; following this there is a decrease in the percentage of reticulocytes and by the twenty-first

\*The reticulocytes were stained and counted in the following manner: A 0.3 per cent solution of brilliant cresyl blue (National Aniline and Chemical Co.) was made in physiological salt solution and filtered through filter paper. The blood smear was prepared upon a cover glass by placing a drop of blood upon one cover glass, dipping a tooth pick into the brilliant cresyl blue solution and then mixing the blue solution adhering to the toothpick with the drop of blood until the blood assumed a bluish tint. Another coverslip was then placed over the stained glass and when the film had spread out evenly the cover slips were quickly pulled apart by slipping them sideways. To secure even distribution of the cells, the cover slips were thoroughly cleaned, first with soap and water, then distilled water and finally alcohol. Just before using them they were polished by vigorously rubbing over a piece of typewriter paper, placed on a flat table. After the smear was dried, it was stained in the usual manner with Wright's stain. The number of reticulocytes observed during the enumeration of the thousand red blood cells was expressed in per cent of the total number of cells counted.

day the number is less than three per cent. After the reticulocyte percentage reaches its maximum and begins to decrease, there is often a second but less marked rise in the percentage before the final diminution starts. In general, it may be said that the maximum height of the reticulocyte increase bears an inverse relationship to the level of the red cell count at the beginning of the treatment as shown by chart II. From the chart it is seen that with an initial red cell count which varies between 0.5 and 2.0 millions per cubic millimeter, the average maximum increase in reticulocytes is approximately 18 per cent; when the initial count is between 2.3 and 2.7 millions per cubic millimeter, the average maximum increase is 8 per cent. when the initial red cell count is between 3.5 and 5.2 millions per cubic millimeter, there may be no significant increase in reticulocytes. This inverse relationship is emphasized further in chart III in which the general curve indicates very clearly that the lower the initial red cell count, the higher is the percentage increase in the reticulocytes. The increase in the percentage of reticulated red blood cells, therefore, is a very constant and reliable criterion of the effectiveness of the liver substance under trial, provided the initial red cell count of the patient is not greater than 3 million per cubic millimeter. Furthermore, when the increase in reticulocytes does occur, it is a very dependable indication that the total red cell count will eventually reach normal with further appropriate treatment, unless some unusual complication arises. Chart IV indicates changes in the peripheral blood of a patient

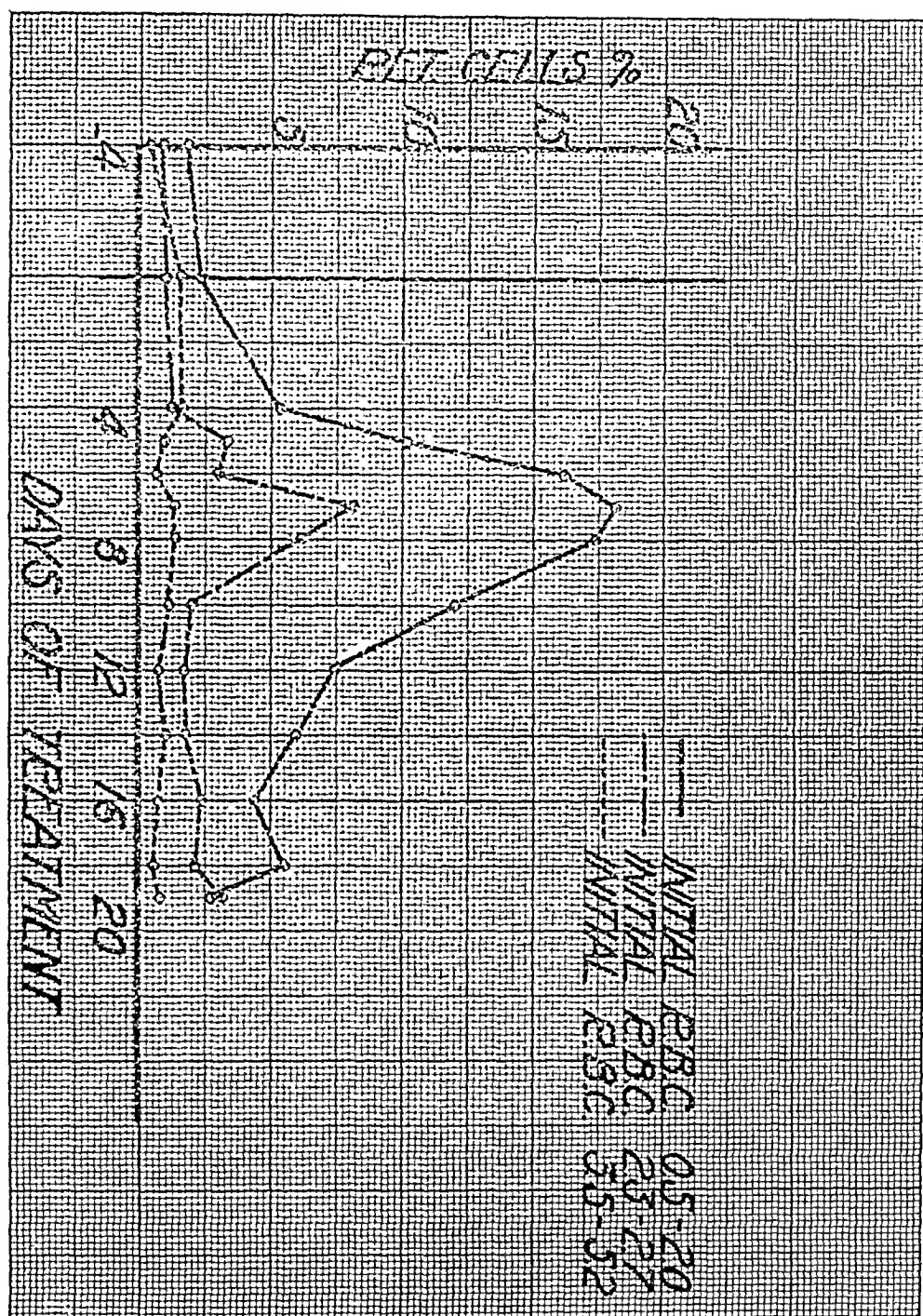


CHART II.—Curves showing the average daily change in the reticulated cell count after instituting liver extract therapy in 18 patients whose initial erythrocyte count ranged between 0.5 and 2.0 million cells per cu. mm., 4 patients with initial erythrocyte counts between 2.3 and 2.7 millions and 2 patients with erythrocyte counts between 3.5 and 5.2 millions.



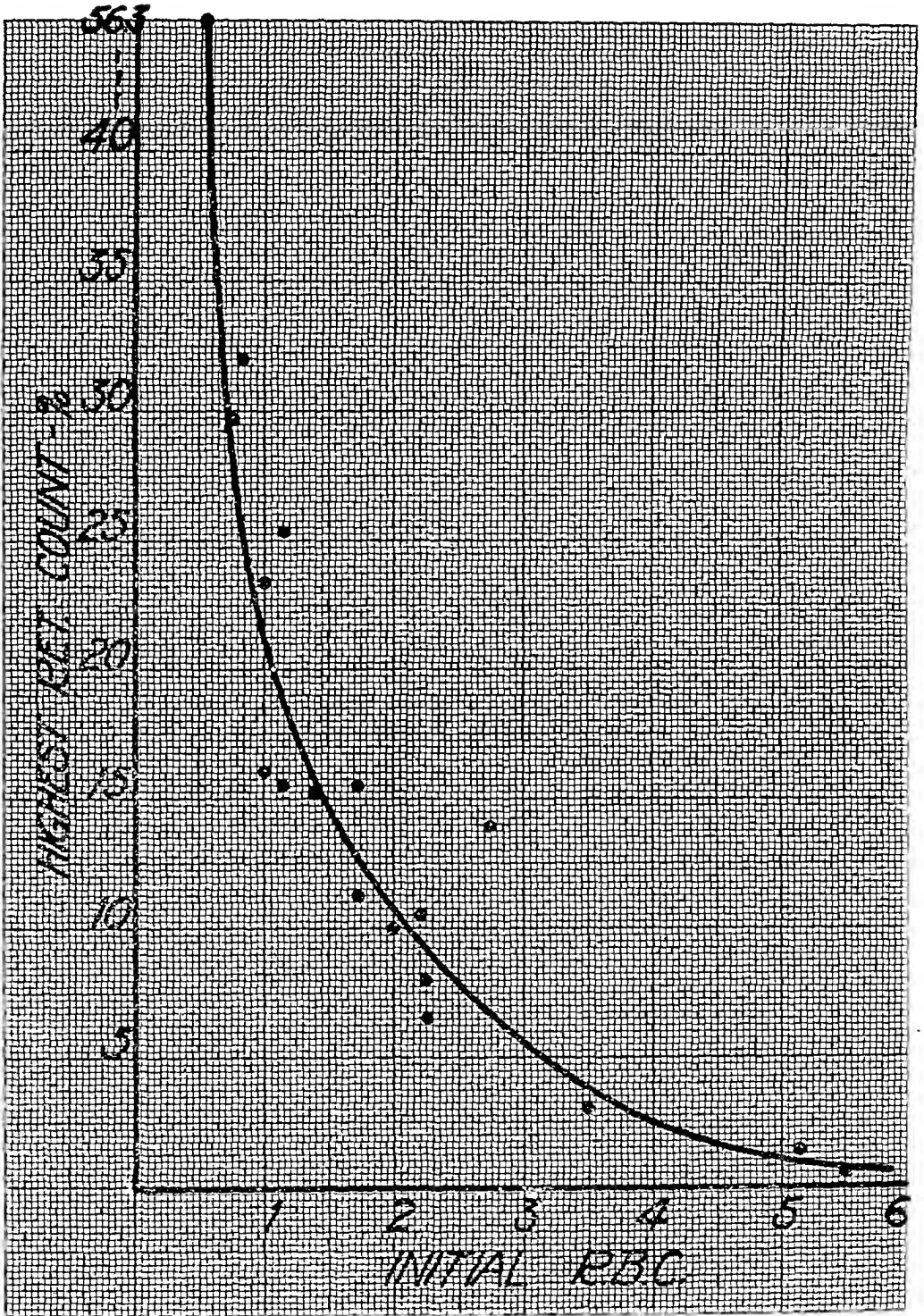


CHART III.—The maximum rise in reticulocytes (per cent) shown by 28 patients whose initial erythrocyte count is indicated by millions per cu. mm. on the abscissae.

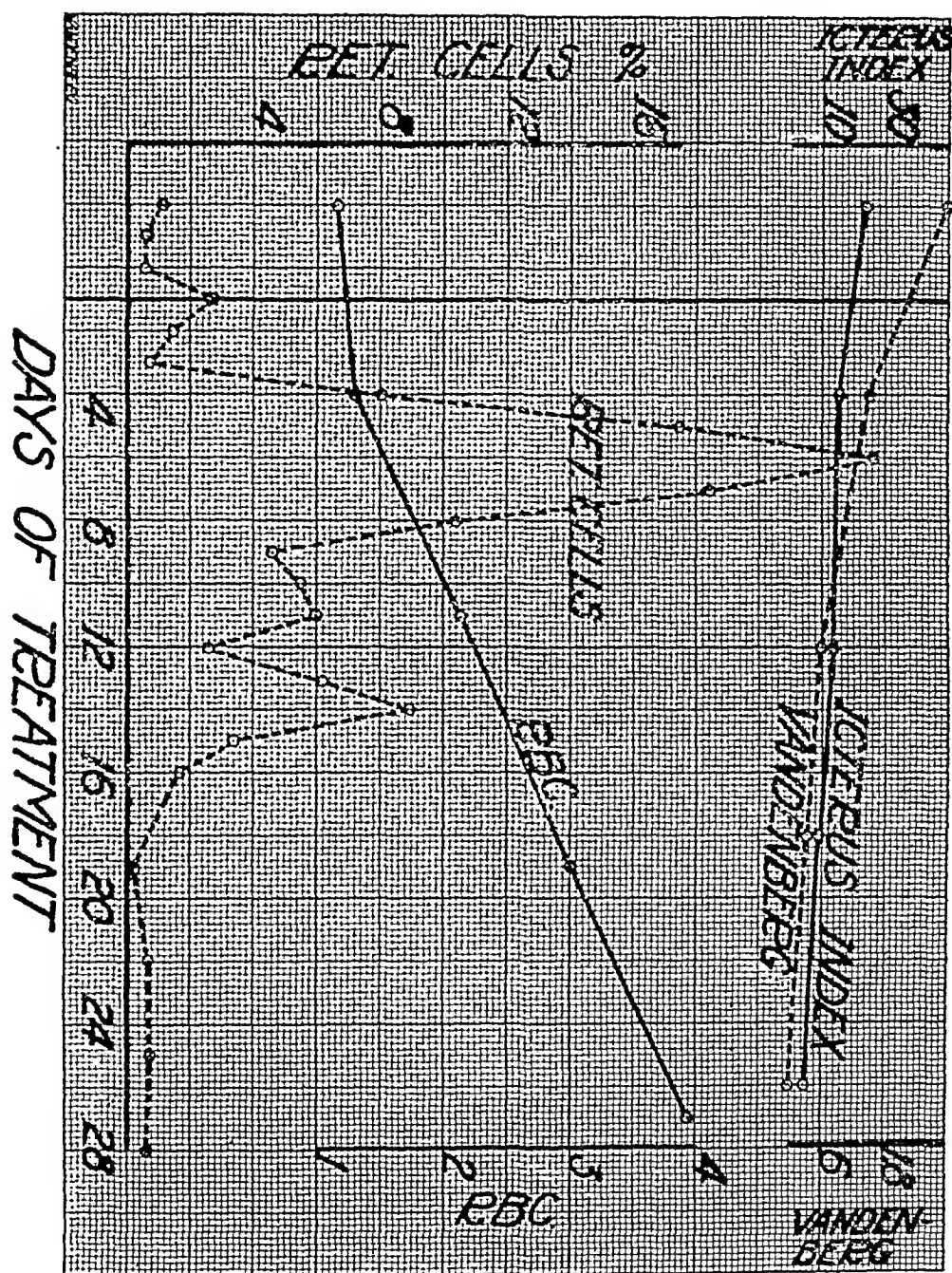


CHART IV.—Daily changes in the blood examination of a representative case of pernicious anemia taking liver extract. R.B.C. = millions of erythrocytes per cu. mm. Ret. cells = per cent reticulocytes. van den Bergh = mgs. bilirubin per 100 c.c. of serum.

with pernicious anemia before and after daily administration of an amount of liver extract which is equivalent to one pound of liver. Patients having an initial erythrocyte count equal to that of this patient may be expected to show changes chronologically and quantitatively similar to those given in this chart, provided there are no unusual complications present.

The greater increase in the percentage of reticulocytes when the red blood count is low than when it is high, appears to be a function of the special pathology of the bone marrow in pernicious anemia. As Peabody (8) and others have shown, the bulk of the erythroblastic tissue in the blood forming areas is in the megaloblastic, macro-normoblastic and normoblastic stage. This, in fact, appears to be the specific hemopoietic lesion—a failure of the erythroblastic cells to mature to the adult state. The “stimulus” given either directly by the liver material or indirectly through the action of the specific agent on other tissues, secretions or in some unknown manner, causes the cells to proceed with their development. A greater number, therefore, reach the reticulocyte stage than previously and this is reflected in the peripheral circulation by an increase in the percentage and absolute number of reticulocytes. The greater the amount of erythroblastic tissue in the nucleated stage, the greater will be the number of reticulocytes produced when the rate of maturation becomes more normal.

The cause of the second rise in the number of reticulocytes after the “peak” had been reached and the number and percentage had started to decrease, offers material for speculation.

It was a fairly common phenomenon in the series studied. Whether this may be explained by assuming that the marrow of a different group of bones was affected or whether this is an unexplained but purely physiological response is a matter for future study.

With the increase in the number of red blood cells in the peripheral circulation, anisocytosis and poikilocytosis become less marked. Following the administration of liver extract, it was observed that the mean diameter of the red blood cells returned to normal or less than normal. This same change has been noted by Medearis and Minot (9) in the blood of patients with pernicious anemia after the feeding of whole liver. Poikilocytosis disappears rather slowly, and some abnormally shaped forms persist to a greater or less degree until the blood count is almost normal. It is suggestive that this phenomenon is not entirely a function of the crowded condition of the bone marrow, but rather related to some other feature of abnormal blood formation.

Coincident with the rise in the number of red blood cells after feeding liver extract, the number of white blood corpuscles rapidly increases to normal or the upper limits of normal. The cell morphology also approaches that of the normal blood. A detailed study of this, which is now in progress, will be published elsewhere. There is a tendency for the blood platelets to increase in number, approaching the normal and at times even greater.

It has been observed by a number of investigators (2) (7) that accompanying the rise in the red blood cells as a result of whole liver feeding, there

is a decrease in the excess of bile pigments of the blood plasma. We have noted that all patients with pernicious anemia have an increase in the bilirubin of the plasma during a relapse as indicated by the icterus index and the van den Bergh reaction. After the administration of the liver extract there was a return to normal within a few weeks and with this there was a disappearance of the yellowish tint to the patient's skin. Furthermore, both the van den Bergh reaction and icterus index gave subsequent normal readings in all patients except a few who suffered a relapse from various causes.

#### MAINTENANCE DOSAGE OF LIVER EXTRACT.

It has been our practice, in treating patients with pernicious anemia, to give the liver extract in amounts equivalent to one pound of liver daily until the blood reaches normal. After it has remained at this level for a period of three or four weeks, the dosage has been reduced to the equivalent of one-half pound daily. Further reduction in the dosage is probably possible but the exact amount which is necessary to maintain the blood at a normal level has not yet been determined, and it is entirely possible that this dosage varies with the individual patient. It is not unlikely that as small an amount as the equivalent of one-fourth pound or less daily may be effective. In one patient who was under our observation for a long period, the dosage was reduced to the equivalent of one-half pound of liver a week. This was obviously insufficient as there was first

a rather striking diminution in the hemoglobin percentage of the blood which was followed within two weeks by a drop in the red blood count from normal to two million cells per cubic millimeter.

Under ordinary conditions, in the treatment of patients with uncomplicated pernicious anemia, the only other factor in addition to the liver extract which is essential, is an average well-balanced, normal diet. This may usually be left to the patient's own discretion and the keen appetite which is associated with the general improvement. As Minot and Murphy (2) have stated, an excess of fat in the diet does not prevent the regeneration of blood in patients with pernicious anemia following the administration of liver extract. This is illustrated by one of our own patients who ingested daily a weighed diet, composed of 40 to 50 gms. protein, 200 to 250 gms. fat and 100 to 230 gms. carbohydrate. At the beginning of the observation period, the red blood count was 1,780,000 per cubic millimeter. The patient received liver extract in an amount equivalent to one pound of liver daily and the diet as outlined above, for fourteen days. At the end of this time the red blood count was 4.64 million per cubic millimeter and there had been a typical increase in the reticulated red blood cells, which showed the initial rise on the fourth day of treatment, reached its peak of 17.8 per cent on the sixth day, and decreased to below 3 per cent on the thirteenth day. In two other patients with pernicious anemia there was a similar satisfactory response following the administration of liver extract during which time the pa-

tient received a diet high in carbohydrate and lacking in fresh fruits, fresh and canned vegetables and red meats.

No attempt has been made to administer the liver extract by other routes than by mouth except in the case of one patient who received the equivalent of one pound for ten days per rectum. In this patient the reticulated cells rose from 1.0 to 5.6 per cent on the sixth day, which indicated an inconclusive or perhaps slightly successful result.

Two patients who had a cystitis when they came under our care failed to show a rise in the reticulocytes or hemoglobin and erythrocytes when given the liver extract. In another patient the hemoglobin decreased 14 per cent and the erythrocytes diminished slightly while taking the liver extract during a severe upper respiratory infection. Before the onset of the infection the patient's erythrocyte count was three million cells per cubic millimeter so that a rise rather than a fall in the number of red blood cells was anticipated. These observations seem to indicate that acute or chronic infections may inhibit blood regeneration in pernicious anemia despite adequate liver or liver extract therapy.

In a series of pernicious anemia patients having signs and symptoms of combined posterior and lateral cord tract degeneration, it has been noted that the administration of liver or liver extract produces no immediate change in the advanced neurological symptoms although blood regeneration seems to follow the usual course. In certain cases with very early signs of cord involvement, we have noted improvement in the neurological symptoms after the

institution of treatment with liver extract and physio-therapy procedures which were designed to strengthen the muscles and develop their control. At present we believe that the prognosis in this complication should be guarded but the results of the changes in the nervous system should not be considered as entirely refractory in every case to appropriate treatment.

#### SUMMARY.

1. A liver extract, prepared according to the method of Cohn, Minot, et al, has been found to produce the same effects on the regeneration of blood in 28 patients with pernicious anemia as previously have been noted to follow the administration of one-half pound of liver daily.

2. The earliest indication of blood regeneration following the use of this extract is a rise in the number of reticulocytes of the peripheral blood. This rise begins between the third and sixth day, reaches a maximum about the eighth day and the percentage returns to approximately normal limits by the end of the 21st day. At about the tenth day the erythrocyte count and the blood hemoglobin begin to increase. As a rule the blood picture has returned to normal by the end of the sixth to eighth week of liver extract therapy.

3. The earliest clinical signs of improvement are increased appetite and sense of well being, often appearing as early as the third day of liver extract therapy and usually by the end of the fifth day.

4. It has been noted in three pa-

tients with active infections that no improvement followed the administration of liver extract as long as the infection persisted.

5. Improvement in the signs and symptoms of combined posterior and

lateral sclerosis of the spinal cord did not parallel the regeneration of blood, although slow improvement in the neurological condition has frequently followed the combined use of liver extract and physiotherapy.

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# The Evolution of the Modern Treatment of Pulmonary Tuberculosis\*

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**I**N the treatment of disease there is always occurring an ebb and flow in the tide of medical opinion and out of this is finally evolved the accepted standard of practice.

I would ask your attention today to a resume of this evolution insofar as it affects the treatment of Pulmonary Tuberculosis.

Much of the therapeutic teaching of any period is discarded in thirty or forty years as not standing the test of experience or not having a reliable scientific foundation and much of our present day treatment we may be sure will go on the scrap heap in the future; yet, out of a kaleidoscopic array of remedies and measures, there emerges now and again one so well founded and so successful that it becomes a permanent addition to our armamentarium. Thus, step by step, with many backward steps, has evolved the modern treatment of pulmonary tuberculosis. Looking over the ground we see that up to the time of Laennec in the second decade of the last century there was little if anything of the prevailing treatment which we should care to preserve and the foundation for the evo-

lution of which I am speaking can be said to have been laid by his work.

That no intelligent treatment had been developed up to that time is natural enough since there was no thorough knowledge of the pathology of the disease on which to found a reliable diagnosis and a purposeful treatment.

When, however, Laennec, one of the very greatest minds that medicine has ever produced, in the second decade of the last century elucidated its pathology at the autopsy table and, at the bedside, showed the profession by his discovery of auscultation and by building up of the art of physical examination how to make a diagnosis, the eventual development of a rational treatment was assured.

The profession did not have to wait long for the advance to begin. Brilliant minds stimulated by his work were eagerly studying the tuberculosis problem and in the fifties the first fundamental step toward a rational therapy was taken when Hermann Brehmer at Goerbersdorf evolved the Hygienic, Dietetic and Sanatorium treatment which will always be connected with his name. That his method at first had many faults, does not detract from the honor we owe him and when developed and corrected by his brilliant pu-

\*Presented before the American College of Physicians, March 6, 1928, New Orleans, La.

pil Detweiler at Falkenstein, it became the basis of our modern treatment, and we are too prone to forget the great debt we owe these two pioneers. Thus by the sixties and seventies there began to be a rational and successful treatment carried out in sanatoria in Germany, if not elsewhere, and yielding hitherto unheard-of results. However as is usual in our profession, it was years before the method was generally recognized and applied, largely for lack of Sanatoria, and when in 1895 I was seeking for guidance in building my plan of treatment I had to turn to German authors for light on the method, but there I found it laid down with that beautiful if somewhat meticulous accuracy which is the German gift.

While all this time the knowledge of tuberculosis was increasing enormously, the problem of its etiology was still unsettled and without a knowledge of the cause of a disease its treatment is always handicapped.

True in 1865 Villemin demonstrated its infectiousness but did not discover the organism, but when Pasteur, in the seventies, laid the foundations of bacteriology the time was ripe for the solution of the problem. When a problem is ripe a man usually appears who can solve it and in 1882 the medical world was astonished when a quiet country practitioner, Robert Koch, announced and demonstrated the discovery of the *Bacillus tuberculosis*. The time seemed ready for the solution of the question of treatment along specific lines and, continuing his researches, Koch before long offered the world, which had suffered so cruelly from this scourge for milleniums, a new remedy,

Tuberculin, resting on careful reasoning and scientific research and apparently verified by thorough experimental work.

The profession, and indeed the whole world, eagerly grasped at this long awaited specific which was to solve the therapeutic problem and to cure formerly hopeless cases out of hand. It was met by an enthusiasm which it is hard today to realize. Those of us who are old enough can recall the breathless excitement with which the promise of such a remedy was met everywhere. Well do I remember how, as House officer in St. Luke's Hospital, New York, I saw that fine clinician and acute diagnostician Francis P. Kinncutt almost reverently open the first packet to reach New York from Germany and what hopes filled our hearts. But that was nearly forty years ago and today the question of its value and the indications for its use are still subjects for debate and still unsettled and tuberculin cannot as yet be ranked as a permanent addition to our therapeutics in pulmonary tuberculosis though some men still cling to it. Used at first in dangerously large doses and not fully understood, the early results were anything but encouraging and when the reports from Virchow's autopsy table began to come in with their tales of inflammation of tuberculous tissue and generalization of the process there was a strong reaction from the earlier enthusiasm, which almost stopped its use. However, much careful work, especially by Petruschky, developed a better method of dosage and application which opened a long period, lasting through the first decade of this century, when it was in very



general use. But though all of us who have applied it have recognized its latent possibilities and have seen some brilliant cures, clear indications for its use in pulmonary tuberculosis have not yet been worked out and while, as I said, a few still have confidence in it, the general consensus of feeling among special workers is that, in spite of its value in certain other forms of tuberculosis, in pulmonary tuberculosis, save in a few selected cases, it is a disappointing and at times a dangerous remedy and while it is still being studied and while we all hope that some successful modification of it will be discovered, tuberculin for pulmonary tuberculosis is for the present in eclipse. However, though it cannot, I believe, be as yet recognized as one of the permanent additions to our therapeutics it has served as a splendid stimulus to the scientific study of the tuberculosis problem and has thus been indirectly of immense value. Many sera of which I would mention only those of Marmorek and Maragliano have been strongly advocated as have some vaccines, but none has been able to hold the field or to win a permanent place in the profession's confidence. However, I cannot fail to mention the recent distinguished work of Calmette on B. C. G. for the immunization of infants. Backed up by his great repute as a scientist and an honest man and by a very large series of cases in France and in the Latin countries, it may well be that it will be proven to offer us a solution of the problem of the immunization of infants. But the physicians in other countries have naturally been very cautious in feeding live, even if attenuated, bacilli to babies. At present it

can only be called a very promising investigation on a large scale by an able and honest man which calls for further study.

But while the line of investigation opened up by Koch, which we hoped would carry the evolution of treatment further, has disappointed us, there developed just about the same time in Italy what has proved to be one of the most brilliant advances ever made in phthiseotherapy. I refer to Forlanini's artificial pneumothorax. I say Forlanini's for he unquestionably deserves the credit as the real pioneer and developer of this treatment and his name should always be connected with it just as much as that of a surgeon with a special operation which he has perfected or a physician with a disease whose secrets he has uncovered. First brought out in 1884, the profession, as usual, was slow to give it attention or adopt it though Murphy of Chicago in the early nineties did excellent original work on it. However, it was chiefly brought to public attention and developed in Germany, Sweden and Denmark, and it was not until 1910 that it began to be practiced in this country. But today it is universally recognized as a valuable and reliable procedure and has given us results undreamed-of before in a certain class of severe cases and has become an essential measure in the cure and a permanent addition to our treatment. But there were many cases, where either on account of adhesions, or for other reasons, pneumothorax had failed or had not been applicable, and where the physician, feeling his helplessness, longed to do something more for his apparently hopeless cases. In science even

as in business demand makes supply, and about the end of the last century surgeons, led at first by Tuffier in France and later in Germany by many able workers, among whom Wilms and Sauerbruch stand preëminent, began to develop pulmonary surgery which has most brilliantly met the need of these cases and after much experimental work with various operations and indications we have in Thoracoplasty, Apicolysis, Phrenectomy, and Phrenicoexairesis well planned measures with a moderate mortality which have added to the list of curable cases a further number of hitherto utterly hopeless patients. These operations form a further permanent addition to our means curing tuberculosis and have made the doctors' task much less difficult and heartrending.

During all these years drugs, which were at first a recognized part of the therapeutics of tuberculosis, have been steadily losing ground save as adjuncts or as symptomatic remedies, when they can be invaluable, and about which the modern doctor knows much too little. However, as cures for pulmonary tuberculosis they are no longer used with the enthusiasm and faith which once marked the profession's attitude to them and no doctor would today claim that he could cure tuberculosis by any drug but rather only that he could benefit the patient by the use of them. Ehrlich's brilliant work on the chemotherapy of syphilis has made the profession hope that some patient experimental chemist will yet discover for us a specific drug, and when Mollgard quite recently made such a claim

for Sanocrysin the profession hoped again, but is already disillusionized.

Another remedy which has many centuries or possibly milleniums of an unsystematic use behind it, and which has lately been brought back to popularity by Rollier in Leysin is Heliotherapy. But while certain doctors, some of Rollier's assistants and the workers at Pearysburg and others, use it in cases of pulmonary tuberculosis, Rollier himself told me last year that he did not advocate it in pulmonary cases and most men consider that it is likely to activate sleeping trouble and do harm. However, its results in surgical and glandular tuberculosis such as you see at Leysin are some of the most brilliant that I have ever seen in therapeutics anywhere and it is to be hoped that workers with this means will be able to demonstrate its applicability as a builder of tissue resistance and a fortifier of the constitution, not merely in surgical but in pulmonary tuberculosis. Certainly I have never seen such splendid vitality in tuberculous people as is seen in Rollier's patients. Their skin is almost bursting with health and blood and a comparison of the patients who have been there already some time with their superb appearance of health, their color, their nourishment, their cheerfulness, with the new patients recently come in with their sad, sick faces, their bad nutrition and pallor and their general look of bad resistance, is astonishing and I would give all I have if I felt I could use it in my pulmonary cases as he does in his surgical ones. Whether the sunlight itself or the mere exposure to the fresh cold air or some other factor is the chief thing in the results is not

yet settled. Certainly at Pearysburg, where sun is as often lacking as not, the results are excellent and much more work must be done on this question before it is settled, but there is no fear that so powerful a modality will ever be abandoned. Further, in the quartz light we have an easy means of getting many of the effects of the sunlight indoors if the wind out doors is too strong, while, especially in tuberculous enteritis, it is yielding us results such as we never hoped could be possible, and which have changed our ideas of the prognosis of this terrible disease.

Older probably than any other treatment, Climate has been relied on in pulmonary tuberculosis for endless years. Once unduly vaunted and expected to work miracles, which it often did, the failure to use it with intelligent care justified Osler's wise dictum that "care without climate is better than climate without care" and this abuse of a valuable measure is responsible for its today being unduly disregarded. However, it has too many centuries of good clinical results to its credit to need to apologize for itself; foolishly overpraised and blindly trusted in the past it is paying for this by the underpraise and distrust of many today, but it remains, when wisely chosen and well applied, one of our very best aids in restoring that deficient tissue resistance of the tuberculous patient which is the chief aim of all treatment and after watching its effects for many years in many patients, and, best of all, after actually feeling it in myself, I am sure that self interest is not clouding my judgment when I assert that so valuable a means of restoring the fighting

power of the body depleted by the toxins of the tubercle bacillus, will never be abandoned, though we shall doubtless go through recurrent eras of scepticism and over-enthusiasm on the subject. I cannot reject the evidence that I have collected through long years which proves to me that, granted proper conditions, our results in the treatment of pulmonary tuberculosis can be enormously improved and many otherwise hopeless cases saved when they can add properly applied climatic care to their treatment.

There is another method which is essential in the treatment of pulmonary tuberculosis. I refer to Psychotherapy. Although we doctors frequently neglect the psychology of our patients we all of us recognize its importance. The patient is not merely a body to be treated but a mind and soul, to be rebuilt and fortified, and whose condition deeply influences the body; indeed the patient's mentality often dominates the whole case. However, I think this is so well understood by the profession that it is enough to mention it, even though I may return to it later.

Of all the elements in the treatment of tuberculosis which I have thus briefly mentioned there is one which must always take the first place whatever other methods are used in connection with it. I refer of course to the Hygienic and Dietetic treatment and out of this method, so clearly laid down by its founders, and latterly so carefully studied in our sanatoria there has slowly evolved the central idea of Rest as the most important feature in the treatment of this disease. We have, as I have shown you, other invaluable

methods which will never be given up but, whatever their value, rest, at least in the beginning, and often during a large part of the treatment, is the most essential of them all, and though its application may undergo certain modifications it will always be our chief reliance, even if a specific should be discovered. The development of the use of rest dates back to Detweiler's work at Falkenstein and its general adoption has been due to the spread of sanatoria, for they were the laboratories where the hygienic and dietetic treatment could be applied, studied, tested and developed. Here daily clinical experience taught the profession what wonderful cures could at times be wrought in desperate cases by strict bed rest, hence they began to use it more and more, first tentatively, then enthusiastically and today not a few excessively, so that we no longer need to urge its use but rather to warn against its possible abuse. We doctors are prone to go to extremes with every new treatment and it is natural that some have pushed it too far, but while there are many real dangers in the abuse of rest they are not as great as the dangers of the abuse of exercise which was once so common. The case which has been kept at bed rest for years suffers in his morale, in his outlook on life, his ego becomes exaggerated and often his future usefulness is seriously impaired, if not ruined, and he is made into a useless hypochondriac. These are bad things and an indictment of the doctor who allows them, but exercise in a patient with active trouble, with or without temperature, may cause an activation or a dissemination whose results on his health

and even life can be disastrous; hence in every case, unless indeed it be the most incipient, there is a time for more or less complete rest. Later there comes a time when exercise must be begun and increased and it takes skill and experience to know when this time is, indeed it takes far more skill to use exercise rightly and wisely than to put a patient to bed and keep him there. Moreover when you put him to bed it takes much knowledge of human nature and psychotherapy to keep his mental attitude sane and healthy. Thus the crux of the situation is the proper use of those two things, rest and exercise, and long ago Brown of Saranac excellently stated the safe rule when he said, "Exercise short of the point of fatigue," and more recently Krause in his booklet "Rest" has put the whole matter excellently in the following words, "Always keeping below the point of fatigue is all there is to this matter of rest in the therapy of tuberculosis; all other methods ever advocated in its treatment will not begin to counterbalance the violation of this single rule of rest and exercise; never become tired, or if tired, rest until completely refreshed."

This is not the place to go into the details of the rest treatment but I would only say that in deciding when to use bed rest and how long to continue it and how absolute to make it, when to graduate the patient to a proper reclining chair, when to begin exercise and how to increase it, we should not, as is too often the tendency, use temperature as our chief guide. Temperature, pulse, cough, expectoration, mental attitude, nervous condition, physical signs and X-ray plates must

all be taken into careful consideration. Some afebrile cases with good symptoms will yet show signs of too much activity in the lungs or shadows of an exudative process on the plates and will need prolonged rest till these show distinct tendency to clear up, however good the patient's apparent condition. Other even slightly febrile patients with physical signs of a slight activity and with shadows of a productive, fibrotic process may safely be gotten up in a recliner and, if under close observation everything goes well, they can be begun on from one to five minutes' walks with safety and with excellent effects on their psyche and general well being. The mental quiet which properly conducted bed rest can give, is often more important than the physical; and high-strung, nervous patients are often better on a porch by themselves with no visitors, whereas most patients do better with porch mates and are benefited by moderate company. We are striving to restore our patients to health, happiness and utility and a normal frame of mind and it takes close study on the doctor's part and that individualization which is often spoken of but not sufficiently used to fit the cure to each patient's needs.

I have very briefly reviewed the evolution of the chief measures used in the treatment of pulmonary tuberculosis since the time of Laennec and more especially during the last forty years, and as I look over the ground I realize that despite the very many remedies that have been advocated from time to time, those that have been sufficiently tried and tested, and have won a permanent place, are few. As I have said,

the most important feature of our therapy is the Hygienic and Dietetic treatment, out of which has developed the central feature of our modern practice, Rest. Closely allied to this, as producing local rest, come Artificial Pneumothorax and Pulmonary Surgery, in selected cases. Further, Climate has an assured place as the best restorer of the patient's resisting power. Finally, Psychotherapy, while it too often does not have the attention from physicians which it deserves, is a most important agent which, properly used is powerful for good. Heliotherapy, while invaluable in intestinal and surgical tuberculosis, has not yet won an assured place in pulmonary trouble.

At present then, these are our reliance and, few as they are, the results they yield are remarkable in a large percent of our cases, but there are still too many patients, even among those discovered early, and especially among those who come to us late, who are beyond our power to aid and our treatment must evolve much further if we are to be able to cure them, and I believe that it is towards the development of a remedy based on immunological work to build up the resisting power of the cell that we must labor. Our experience with tuberculin has discouraged us, but in the womb of time lies, I believe, the perfect specific which will some day be discovered and which will make the cell unconquerable by the germ and we must rely upon our research workers, who are now so many, to find it for us.

Meanwhile let us not forget that the measures at present at our disposal,

wisely applied, are daily giving brilliant results.

The longer I treat this disease, the more I realize that these two factors, constitutional resisting power, which we have as yet no scientific means of measuring, but which the physician with experience and judgment can fairly estimate, and moral resisting power which the wise and human doctor well knows how to develop, if it be lacking, are the important factors.

Let the doctor keep this ever before his mind, for as long as he has faith in the possibility of cure he can give hope and fighting power to his patient if the patient is half a man and by such psychotherapy he can accomplish miracles.

Would that some scientific investigator might find the measure of the vital resistance in any case and show us how to develop it. That finally we shall solve this riddle I doubt not. Meanwhile it is in the power of any doctor who takes a live interest in his patient and regards him as a human being and knows how to discover the secrets of his heart, to bring to him aid in his fight such as rest or surgery or climate alone cannot give. Fill our patient's heart with hope and we double the fighting force of every cell in his body. Teach him to smile and we wake up a sunlight in his heart which is the best heliotherapy. Rouse his will power to co-operate with us and our task at once becomes easier. What would the results of our sanatoria be if we could banish the many pitiful and usually concealed anxieties and troubles which are too often gnawing at our patients' hearts and holding them back, and lessening their fighting force.

What discoveries the future may bring to us we cannot know, but while we are far from having attained the control over tuberculosis of which we dream, the results of the modern treatment which I have outlined to you are so good that, granted an early diagnosis and that fundamental resisting power which the majority of our patients have, there is no excuse for pessimism in our attitude save in the minority of cases. The hygienist by his prophylaxis is cutting down its incidence and improving the constitutions of those who may fall its victims. The general diagnostician is infinitely more capable of discovering its early manifestations than the very best man in our profession was thirty years ago, and the therapist, having thoroughly mastered the few but powerful measures at his disposal, is returning more and more well trained, dependable patients to a normal, useful life.

Therefore, in closing, my last word is one of hope and of encouragement. Even did we not expect, as we certainly may, any further additions to our knowledge, such as we received from Brehmer and Forlanini, the profession is learning better and better how to fight this plague. Preventive medicine is achieving results hitherto supposed to be unattainable. The constitutions of our people are being raised to a higher level by better conditions of living. Eager research workers are delving into the secrets of nature and I feel very sure that the problem of the cure of tuberculosis will at last be added to the long list of the problems of those other diseases which, in this wonderful century, the intellect of man has solved to the blessing of the race.

# Rheumatic Fever\*

By JAMES CRAIG SMALL, M.D., *Philadelphia.*

## PART I. *Streptococcus cardioarthritides in Rheumatic Fever*

**I**N January, 1927, I described a new species of streptococcus isolated from cultures of the blood and of the pharyngeal exudate in cases of rheumatic fever, under the name *Streptococcus cardioarthritidis*.<sup>1</sup> This streptococcus does not produce any obvious change in the media adjacent to its colony where grown on the surface of agar medium containing blood. It ferments inulin—an unusual property for a streptococcus—and new strains may readily be identified by agglutination with a monovalent immune serum.

This microorganism is found regularly in throat cultures of patients with rheumatic fever or chorea, and we have isolated it in three instances from the blood of patients with rheumatic fever. It is not confined to a limited geographical area. Cultures have been received from England, and others identified in Bierut, Syria.

Inoculated into animals, it produces lesions of the myocardium, pericardium, and cardiac valves; in the joints, their bursae or within the tendon sheaths; and in the central nervous system. These lesions resemble those found in rheumatic fever. They have been observed in rabbits and in horses.

Agglutinins in the patient's blood

serum in chorea, and acute rheumatic fever have been demonstrated, the titer is low early in the first attack and rises during convalescence, but declines again soon after recovery.

Opsonins for this streptococcus are low in amount in the patient's serum during the acute stage of the disease. They rise during the favorable course of the disease, regardless of the mode of treatment, and persist at a high level during convalescence and following recovery. In fatal cases low titers have been found.

The action of the anti-serum of *Streptococcus cardioarthritidis* has been observed in 251 patients, 121 of whom were treated in the special rheumatic fever wards of the Philadelphia General Hospital. Prompt beneficial effects follow its use in chorea, and in acute rheumatic fever. These occur with regularity and have been observed in the acute arthritis, the endocarditis, the myocarditis, the pericarditis, the pleuritis, the pneumonitis, and the subcutaneous nodules of rheumatic fever. In chorea, the purposeless twitchings subside promptly and usually disappear within a week after the injection of the serum.

The protection conferred by the anti-serum probably lasts from four to five weeks as judged by the few relapses which occurred early in the

\*Read before the American College of Physicians, March 7, 1928, New Orleans, La.

work. This is in accord with the length of the period of passive immunity conferred by other therapeutic anti-sera. To prevent such relapses it is necessary to begin active immunization with the vaccine, soon after the administration of the anti-serum.

Individuals with deep seated rheumatic infections are extremely susceptible to small doses of the vaccine of *Streptococcus cardioarthritidis* injected subcutaneously. They react with exacerbations of the joint symptoms accompanied by febrile reactions, anorexia, loss of weight, abdominal distress, tympanites, nausea, vomiting, precordial pain, cardiac irregularities, muscular twitchings, emotional instability, wakefulness, an increase in leukocytes, and a depression of the opsonic index. Not all of these arise in a particular patient, those appearing depending on the severity of the reaction

and on the prominent existing rheumatic lesions. Convalescent cases of acute rheumatic fever have suffered sharp relapses following unduly large doses of this vaccine. These reactions appear to be controlled by the administration of salicylates in adequate dosage. Conversely properly regulated dosage of this vaccine in suitably chosen cases of subacute rheumatic affections renders them free from persistent symptoms. This improvement is attended by an increased tolerance for the vaccine.

Local areas of erythema arise from intradermal injections of the vaccine, or of soluble products of the microorganisms, but these are inconstant and do not furnish a true index of the patient's susceptibility to these products since systemic reactions may arise from an injection which gives no local reaction.

## PART II. *The Present Development of the Biologic Products of Streptococcus Cardioarthritidis and their Application in the Treatment of Rheumatic Fever.*

The anti-serum of *Streptococcus cardioarthritidis* is being prepared both in horses, and in cattle. The bovine and equine anti-sera appear to be equally effective in the treatment of patients. They have been either monovalent or bivalent, being prepared from one or the other, or from both of the two strains first isolated in blood cultures. One of these strains ferments lactose. The other does not—nevertheless their monovalent anti-sera act interchangeably when applied in patients.

Bovine anti-serum has an advantage over equine in that it produces very mild symptoms of serum sickness. It is the exception to have troublesome

urticaria following the use of bovine serum, while febrile reactions and arthralgia are rarely observed. It is important to avoid severe serum sickness in the treatment of rheumatic fever, since the arthralgia attending it may be confused with a relapse of the arthritis of the rheumatic fever.

The different lots of anti-serum tested during the course of the development of this product have had to be used in amounts varying from 25 c.c. to 200 c.c. in bringing about comparable clinical responses. The anti-serum (equine) has been concentrated by the globulin precipitation method. This product is required in dosage of from 10 to 20 c.c. depending on the



severity of the case. The concentrated bovine anti-serum is in process of preparation.

In the application of the anti-serum in the treatment of the patient, two contingencies must be guarded against. These are hypersensitiveness to the serum of the species employed in its preparation and local reactions of a specific nature arising from the local inflammatory reaction of immunity upon union of antigen and antibody in the diseased tissues. The former may be determined by intradermal skin tests, the latter can be avoided by the broken dose method of administering the anti-serum and by injecting it subcutaneously or intramuscularly. Not more than 5 c.c. of the concentrated anti-serum should be injected as the first treatment. This is followed by another 5 c.c. after 8 to 12 hours and if more is necessary 5 to 10 c.c. may be injected after another 18 to 24 hours.

The vaccine of *Streptococcus cardioarthritidis* is more difficult to apply clinically, due to the ever present danger of over dosage, and to the appearance of delayed general reactions which may reach their height at from 10 to 14 days after an injection of the vaccine.

To eliminate this secondary reaction the use of the vaccine has been discon-

tinued in favor of soluble products of the micro-organisms. This latter has been designated, soluble antigen. It acts in a manner similar to the vaccine in building active immunity. It is a normal saline extract of the bacteria and is used in two dilutions—a 1:10,000 and a 1:1000 dilution. The initial dose of the 1:10,000 dilution is not greater than 0.1 c.c. subcutaneously. The 1:1000 dilution is reserved for follow-up treatment after a course of the more dilute product, or it may on occasion be used in patients who have recently received adequate amounts of the anti-serum.

The dosage of soluble antigen should be regulated so that an injection will not excite severe local reactions lasting five days or more; so that no febrile reactions occur; so that a persistent acceleration of pulse is avoided; and so that the patient does not lose body weight while under treatment.

Patients with chronic rheumatism are found in the chronic arthritis group and may be identified by the subcutaneous injection of 0.05, or 0.1 c.c. of the 1:1000, soluble antigen. Patients with chronic rheumatism will show marked general and focal symptoms following such an injection. This procedure constitutes a safe diagnostic test.

# Tularemia (Francis' Disease)\*†

*A Clinical and Pathological Study of Forty-Eight Non-Fatal Cases and One Rapidly Fatal Case, with Autopsy, Occurring in Dayton, Ohio.*

WALTER M. SIMPSON, M.S., M.D., F.A.C.P., *Dayton, Ohio.*

THE history of tularemia makes fascinating study. It is, in every respect, "the first American disease." The physicians of this country should be thrilled by the thought that not only was this disease discovered by American investigators, but also because its specific etiologic agent, the determination of its modes of transmission from animal to animal and from animal to man, the descriptions of its clinical manifestations and its pathology and bacteriology, were made known by American workers. And leading all, as the guiding spirit which has made this accomplishment possible, is Edward Francis, of the United States Public Health Service. No greater tribute could be paid to the officers of this Service than Vaughan's statement (1) that tularemia is "a disease discovered by the United States Public Health Service." No less than twenty-five contributions, concerned directly with this disease, have appeared in the Public Health Reports.

During the summer of 1907, Martin, an ophthalmic surgeon of Arizona, had observed five human cases

of a disease which he attributed to an infection resulting from the skinning and dressing of wild rabbits. In three of these, the primary localization was in the eye. In 1925, Dr. Frederick G. Novy, Professor of Bacteriology at the University of Michigan, found in his files a letter from Martin, dated September 19, 1907. Dr. Novy marked the letter "tularemia" and sent it to Dr. Francis. It stands as the first description of cases of tularemia in the human:

Phoenix, Territory  
of Arizona,  
September 19, 1907.

Dr. Frederick G. Novy,  
Ann Arbor, Michigan.

Dear Doctor:

There have been during the summer several individuals in this locality who have suffered from an infection as a result of skinning and dressing wild rabbits. They were of the so-called "jack" variety. Three of these persons have had their primary lesions in or about the eye. Small abscesses formed in the lids and on the bulbar conjunctiva as well. In one case the cornea was involved, the preauricular gland being involved, as well as the anterior cervical and the submaxillary. At the onset there were chills, profuse sweating and an elevation of temper-

\*Presented, in part, before the Annual Clinical Session of the American College of Physicians, New Orleans, March 7, 1928.

†From the Pathological Laboratories of the Miami Valley Hospital, Dayton, Ohio.

ature of from two to five degrees, with rapid pulse, lasting several days. The glands suppurated and all were evacuated. In one case a nodular condition of the lids still remains. There were no deaths; in fact, the illness was not profound. In one instance the infection took place in the foot, and others in the hands, etc., the adjacent lymphatics, of course, being involved.

Yours very truly,

Ancil Martin, M.D.

Francis found anti-*tularensis* agglutinins still present in one of Dr. Martin's cases eighteen years after the original infection.

In 1910, Pearse, (2) of Brigham City, Utah, described nine cases of a disease of man which was for several years popularly known as "deer fly fever." To Pearse, then, should go the credit for having first described the *clinical manifestations* of the disease which was called *tularemia* by Francis nine years later. All of Pearse's cases followed horse-fly bites on some exposed part of the body, and all occurred during the month of August. There was one fatality among the cases described by Pearse.

McCoy and Chapin (3), of the Public Health Service, had, in 1911, isolated the specific organism from ground squirrels (*Citellus beecheyi*) dead or dying of a "plague-like" epizootic in Tulare county, California. They gave to the organism the name *Bacterium tularense*, after the county in which their discovery was made.

In 1914, Vail (4), of Cincinnati, described a case of *Bacterium tularense* infection of the eye. In 1915 and in 1917, respectively, Sattler (5) and

Lamb (6), likewise of Cincinnati, described cases of "conjunctivitis *tularensis*." In each instance there was a definite history of the patient having dressed rabbits, and the primary lesion in each instance was on the conjunctiva. In all three of these eye cases, *Bacterium tularense* was isolated by Wherry and Lamb (7). Vail's case, therefore, is the first instance on record in which the disease was diagnosed *bacteriologically*. Wherry and Lamb later (8) isolated *Bacterium tularense* from two wild cottontail rabbits found dead in southern Indiana near the residence of the patient whose disease was described in Sattler's paper.

It was Francis who discovered the unity of the "plague-like disease of rodents" described by McCoy and Chapin and "deer fly fever," the very severe infectious disease of man described by Pearse. In 1919, Francis (9) established a field laboratory at Delta, Utah, in order to investigate the disease then called "deer fly fever." He isolated *Bacterium tularense* from seven human individuals, one of whom had become fatally ill and all having been bitten by the deer fly, *Chrysops discalis*, commonly found on horses. He isolated the same organism from seventeen wild jack rabbits, shot or found dead, and from one ground squirrel. To this new disease of man he gave the descriptive name *tularemia* (10). During this investigation, Francis, as well as Mayne, who worked with him in his field laboratory, acquired the disease. After they had recovered from the severe illness, Francis turned their misfortune to good account by demonstrating in their own blood anti-*tularensis* agglutinins.

Francis then demonstrated that the disease could be transmitted among laboratory animals by the deer fly, *Chrysops discalis* (11).

*"Rabbit Fever" Among Market Men*—Market men have known of this disease, as "rabbit fever," for at least 25 years. The writer has talked with 6 market men who have known of the disease for at least this period of years. One Dayton wholesale poultry dealer has been dealing in rabbits for twenty-one years. In 1908 he acquired tularemia and was told at that time by a wholesaler from St. Louis that he had known of several similar cases in Missouri which had occurred during the 5-year period prior to the onset of the Dayton dealer's illness. After 19 years and 4 months anti-tularensis agglutinins still persist in relatively high titre (1:160) in the blood of the Dayton market man. This case, and that reported by Dr. Ancil Martin, constitute the oldest cases on record. The Dayton case is the oldest case in the eastern United States.

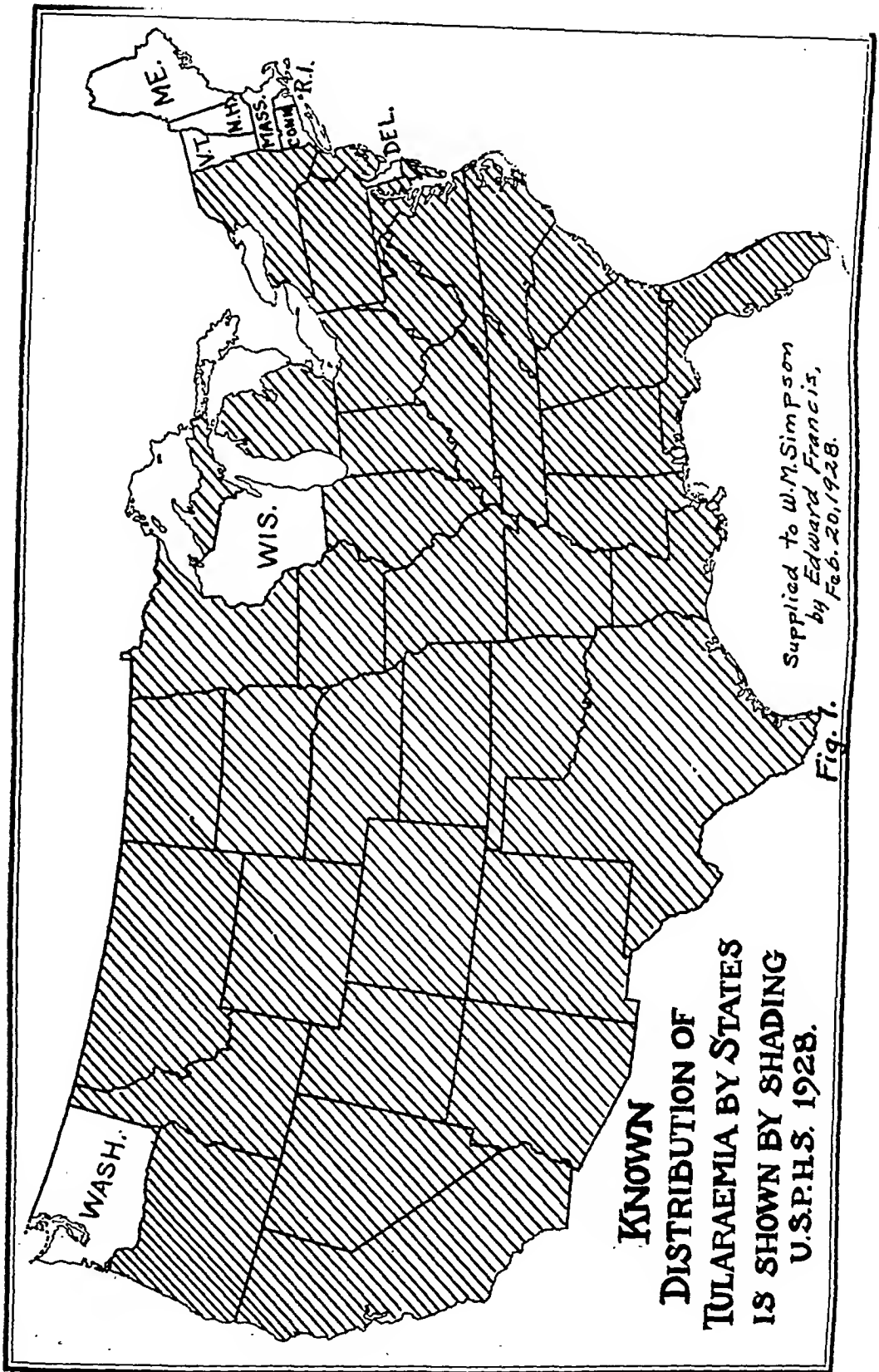
Thompson (12), of Washington, D. C., recognized the first case of tularemia in eastern United States, in a market man who had dressed wild rabbits during November and December of 1921. Thompson was told by his patient that he had "rabbit fever" and that "rabbit fever" had long been known among market men. Francis (13) isolated virulent *Bacterium tularensis* from 7 of 914 rabbit livers collected in a Washington, D. C. market in January, 1923. He also isolated the organism from the rabbit livers gathered at the same market in December, 1924, and December, 1925. Twenty-

two human cases of tularemia have been traced to contact with rabbits sold in this one market.

#### *Identity of Ohara's Disease and Tularemia*

Francis and Moore (14) thoroughly investigated a report by Hachiro Ohara: "Concerning an Acute Febrile Disease Transmitted by Wild Rabbits: a Preliminary Report" which appeared in Jikken Iho, a Japanese journal, in March of 1925. After reviewing Ohara's epidemiologic, clinical, bacteriologic, pathologic, and experimental observations, Francis was led to believe that Ohara's disease and tularemia were identical. Between March 12, 1925 and July 10, 1925, four articles describing this disease appeared in Japanese medical journals, but in these no reference was made to tularemia. Two of the Japanese investigators acquired the disease while performing necropsies of infected laboratory animals. Here we have another example of the almost inevitable occurrence of the infection among laboratory workers engaged in investigating this disease. Francis and Moore requested of Ohara sera from the recovered human cases for agglutination tests and fresh human lymph glands for isolation of the organism. These were promptly provided and gave complete serological and bacteriological proof of the identical nature of the disease in Japan, and tularemia.

One interesting incident in the work of Ohara is the transmission of the disease to a human volunteer. Ohara's wife cheerfully volunteered to be inoculated in order to help prove the scientific convictions of her husband. The



heart's blood and tissue-fluid of a rabbit which had been found dead in a district where numerous human cases of this disease had developed, were lightly rubbed into the back of Madame Ohara's left hand, on January 20, 1925. Twenty minutes later, the adherent material was washed off with soap and water. Two days later, Madame Ohara complained of a mild headache and tenderness in the left axilla. On January 24, the temperature rose to  $37.4^{\circ}\text{C}$ . and she complained of general malaise; one of the left axillary lymphnodes became enlarged to the size of a soy bean and the patient was confined to bed. The next day she complained of chilliness, articular pains, headache, a general feeling of languor, constipation, and numbness of the extremities. On the next day an axillary lymphnode reached the size of the end of the index finger and became very tender, and the inguinal glands became swollen and slightly tender. The fever reached its maximum of  $39.8^{\circ}\text{C}$ . on January 26. On February 7, two axillary nodes the size of a pigeon's egg, and several smaller glands were removed at operation; the two large glands had suppurated. Histologic examination of these glands showed round cell infiltration, dilatation of the blood vessels, extravasation of blood, small abscesses, caseation and giant cells. Eight months after the onset of this illness, Francis found that the serum of Madame Ohara agglutinated *Bacterium tularense*.

#### *Mode of Transmission*

In 1924, Parker and Spencer, (15) of the United States Public Health

Service, while engaged in investigations on Rocky Mountain spotted fever in the Bitterroot Valley of Montana, recognized that the common wood tick of that region, *Dermacentor andersoni*, was a host and transmitter of tularemia. They had been led to suspect that this tick was a "carrier" of the disease two years before this, when they found typical gross lesions of tularemia in guinea pigs into which ticks had been injected as a routine test for the presence of the virus of Rocky Mountain spotted fever. In May, 1923, they isolated *Bacterium tularense* from guinea pigs inoculated with adult wood ticks collected from the vegetation in the Bitterroot valley. They likewise found the infective agent to be present in ticks collected from horses, mountain goats, wood chucks, mountain rats and Columbian ground squirrels. They transmitted the infection to rodents by the wood tick, *Dermacentor andersoni*, and by the rabbit tick, *Haemaphysalis leporis-palustris*. Furthermore, they (16) demonstrated hereditary transmission of the infection by female ticks (*Dermacentor andersoni*) through their eggs from generation to generation. They found that tularemia existed in the snowshoe rabbit and jack rabbit of Montana. They (17) showed that 7 of the species of Montana rodents, and the coyote (*Canis lestes*) (18), were susceptible to tularemia. Finally, they (19) demonstrated the presence of anti-*tularense* agglutinins in their own blood and in the blood of four other workers in their laboratory. All six of these laboratorians had acquired the disease while engaged in this work and in three instances the direct cause was infected ticks.

In the number of cases of tularemia reported, Montana ranks second in the states of the Union—fifty-nine confirmed cases. Of this number, 13 are known to be directly due to tick bites and in 10 other instances a tick bite or contamination by tick tissues or excreta was the probable cause. These ticks constitute a permanent reservoir of infection. The infective agent, widely distributed throughout their bodies, has been demonstrated in the lumen of the gut, in the cells of the gut wall, in the Malpighian tubules, in their circulatory fluid, and in their feces. They harbor the infection throughout their lives and carry it over from winter to winter. They constitute ideal transmitters of the infection. Fortunately, these ticks are found in a restricted area in this country—principally in Montana and the nearby states. Likewise the transmission of tularemia to man through the agency of the horse fly, *Chrysops discalis*, occurs in the Northwest, principally in Utah and the surrounding states. Neither the tick nor the horse fly play an important part in the transmission of the disease east of the Mississippi, although a tick (species undetermined) has caused a few cases in Louisiana and Tennessee.

The vast majority of cases of tularemia have been caused by contamination or self inoculation. It is this method of transmission which has obtained in practically every case east of the Mississippi river. Including the cases presented in the present paper, Ohio has reported 75 proved cases of tularemia—more than any other state. Most of the cases have occurred in market men, who have skinned and

dressed wild rabbits; in housewives or servants who have dressed rabbits for the table; in hunters who have dressed rabbits during the hunt; in farmers or ranchers who have picked infected ticks or flies from their horses or cattle, or who have cut up jack rabbits for fish bait, coyote bait or for feed for domestic animals. The score of cases which have occurred among laboratory workers have resulted from handling infected laboratory animals or infected ticks. Every case in the series reported in this paper occurred as a result of self-inoculation.

There is no evidence at hand which would indicate that the disease has been acquired by eating rabbits infected with tularemia. There is some experimental evidence, however, which would lead one to the conclusion that insufficiently cooked rabbit meat might be dangerous as food. Freese, Lake, and Francis (20) took an experimental rabbit dead of tularemia, rolled the pieces usually prepared for the table in graham flour and fried them in grease over a hot gas flame for ten minutes. At the end of this time a brown crust had developed and the meat gave the appearance of being sufficiently cooked. The pieces were then caryed, the successive layers of muscles appearing white and well cooked until near the bone some red streaks of insufficiently cooked muscle surrounded by red juice were seen. The red muscle was injected into two guinea pigs and the red juice was injected into four guinea pigs, all of which died acutely with the characteristic lesions of tularemia. *Bacterium tularensis* is relatively thermolabile. It succumbs in

10 minutes in cultures and in splenic tissue when heated to 56° to 58°C.

No disease has ever claimed so many victims among laboratory workers as has tularemia. Fifteen cases have occurred among laboratorians of the United States Public Health Service. Two cases occurred among the Japanese investigators. Three cases occurred among laboratory workers in the Lister Institute of Preventive Medicine, London, England, after they had autopsied animals infected with cultures of *Bacterium tularensis* which had been sent to the Institute by Francis, for inclusion in their National Collection of Type Cultures (21). To quote from the report of the Great Britain Medical Research Council, 1921-1922: "It was deemed inadvisable to continue the propagation of this dangerous organism in the National Collection." Most of these laboratory cases occurred in physicians who were thoroughly trained in the handling of virulent bacterial cultures. The portal of entry of the organism in these cases is still a matter of conjecture, since most were of the typhoid type, with neither primary lesion nor bubo.

Prior to 1924 but 15 cases of tularemia had been reported. With the exception of the 12 Japanese cases and the three cases occurring in English laboratorians, none has been reported outside of the boundaries of the United States. Cases have now been reported in every state in the Union, except the New England States, Delaware, Wisconsin and Washington. Up to May 1, 1928, reports of 613 authentic cases have come to the attention of Francis (22). This fact has but one significance, namely, that tularemia is

an exceedingly common disease and the physicians of this country have acquired the ability to recognize it.

There is no record of any transmission of the disease from man to man except in the case reported by Harris (23) in which a mother is thought to have acquired the disease as a result of pricking her thumb while dressing the tularemic ulcer of her son, who had been bitten by an infected deer fly.

The disease is unquestionably transmitted from rabbit to rabbit in nature through the agency of blood sucking lice, flies and ticks. In this way the disease is perpetuated. There is no record of the disease having been found in domestic rabbits raised in rabbitries, although such rabbits are very susceptible to experimental inoculation.

#### *Clinical Manifestations*

Tularemia shows remarkable seasonal variation east and west of the Mississippi River. In the western states the onset of human cases corresponds to the season of the greatest activity of the wood ticks and deer flies. *Dermacentor andersoni*, the tick most often responsible, as intermediate host, for the dissemination of the disease in certain states shows its greatest activity during March, April, May, June, July and August, while the deer fly, *Chrysops discalis*, is at the season of its greatest activity from June to September. Furthermore, the jack rabbits are found almost exclusively west of the Mississippi river and no laws prohibit their destruction. Human cases caused by cutting up jack rabbits occur during the months from April to October. East of the Mississippi the situation



is entirely different. Here the incidence of the disease conforms to those months during which the state game laws permit the hunting of wild cottontail rabbits, namely, November, December, and January. Every individual included in the Dayton series acquired the infection during November. This fact has considerable diagnostic importance.

As the result of the analysis of over 500 case reports, four distinct clinical types have been recognized:

1. *Ulceroglandular*, the most common type, in which the primary lesion is a papule which develops at the point of inoculation, usually the finger or hand in cases acquired by direct contact. The papule rapidly becomes painful and swollen and suppurates in the center, liberating a necrotic core and leaving an ulcer about three-eighths of an inch in diameter, with reddish elevated periphery, a necrotic base, and a sharply punched-out border. These patients usually complain, within a day after the onset of the illness, of tenderness or pain in the regional lymphnodes draining the site of inoculation. On examination these glands will be found to be tender and enlarged. Only in rare instances are glands other than the regional glands involved. It is a peculiar circumstance that the glandular pain frequently precedes by about 24 hours any definite reference by the patient to any pain or swelling at the site of inoculation. The ulcer heals very slowly and healing is apt to be delayed if the primary lesion is incised. In every one of our cases in which surgical incision was done the patients invariably felt worse after the incision. There is

abundant clinical evidence to indicate that one should not interfere surgically with the primary lesion. Incision is usually fruitless because the lesion is essentially a granuloma and there is little or no pus.

In the majority of our cases, inoculation occurred as the result of a perforating wound produced by a sharp fragment of rabbit bone. The hands of market men who have dressed rabbits usually show multiple lacerations produced by the sharp edges of broken ribs and long bones.

The skin overlying the enlarged and painful regional lymphnodes becomes reddened and in about one-half of the cases the skin becomes thinned and the glands drain spontaneously. In the remaining half of the cases the abscess does not burrow its way through the skin but the glands remain hard and rather tender for two to five months and ordinarily return slowly to normal size. In several of our old cases, firm enlarged axillary and epitrochlear nodes persisted for many years. In 27 of our cases the axillary mass became fluctuant and surgical drainage was instituted with good results. The patients invariably felt much better after the surgical drainage of the suppurating axillary glands. In 4 of our cases glands other than the regional glands were involved. It is rather difficult to determine whether or not the enlarged nodes in the axilla of the side opposite to the primary lesion were not the result of an infection in the other hand with no visible primary lesion.

Sporotrichosis-like nodular lymphangitis over the forearm and arm has been described in 33 previously re-

ported cases and occurred in 6 instances in our series. In our cases and in most of those described in the literature these nodules were at first firm and freely movable but later suppurated.

The period of incubation varies from one to five days. In the majority the onset occurred on the second, third or fourth day after inoculation. The onset is sudden and may occur while the patient is asleep or while he is in the midst of his work, and is characterized by "grippe-like" symptoms; severe headache, fever, chills and sweats, aching pains in the back and extremities, vomiting and marked prostration. Many patients are delirious from two to five days.

2. *Oculoglandular type.* These cases differ from those described above in that the primary localization is in the conjunctival sac instead of in the skin. Of 22 cases collected by Francis, 19 had unilateral involvement of an eye and regional glands, while three had simultaneous bilateral involvement of both eyes and the regional nodes on both sides, together with enlargement of the upper cervical lymph-nodes. The early manifestations are excessive lachrymation, marked irritation, edema of the lids and surrounding tissues, edema of the ocular conjunctiva and usually a papule on the inferior palpebral conjunctiva. At the same time there occurs enlargement and pain in one or more of the following groups of lymphnodes: preauricular, parotid, postauricular, submaxillary, anterior cervical, and in a few severe cases the axillary group. The same severe constitutional symptoms

are present as in the ulceroglandular type. In many ways, the diseases long known to ophthalmologists as Parinaud's conjunctivitis and *conjunctivitis necroticans infestiosa* (24) are clinically similar to *conjunctivitis tularensis*. Parinaud's original descriptions reads exactly like the present-day descriptions of tularemic conjunctivitis. Parinaud originally ascribed the disease to "a contagium derived from animals" and recent ophthalmological text books state that the etiologic agent is not known (25).

3. *Glandular type.* In this type there is no visible primary lesion. In 9 of our cases the most careful scrutiny of the fingers and hands revealed no grossly visible papule or ulcer. In all other respects the disease simulates the ulceroglandular type. There is abundant clinical and experimental evidence to show that the organism does pass through unbroken skin.

4. *Typhoid type.* In this type there is no primary lesion and no regional adenopathy. Fever is the outstanding symptom. It closely simulates typhoid fever. Most of the cases occurring among laboratory workers fall into this group.

A skin eruption occurs occasionally and may appear anywhere on the body (26). In one of our cases (J. S.) a maculopapular eruption appeared over the upper extremities and neck, while in another (P. S. J.), a maculopapular eruption appeared over the abdomen, thighs and scrotum. In reviewing the literature, the writer was struck by the number of fatal cases which were preceded by a pustular eruption. It would appear as though the develop-

ment of a pustular eruption carries with it grave prognostic significance.

Most cases are characterized by a considerable degree of chronicity. The convalescence simulates that following severe influenzal infections. Three of the Dayton patients worked during their entire illness but in each instance only because they felt forced to do so because of economic demands. Most of the patients were strictly confined to bed for ten days to three weeks. Usually the patient is so weak during the second month that he is unable to exert himself. Many have gone to work during the third month and have been forced to quit and rest for another month or two. Many of our patients have stated that they do not regain their strength for over one year.

The recorded deaths number 23 (3.7 per cent.). Unquestionably many deaths have not been reported. In addition to the one death reported here-with the writer has learned of at least seven others that have occurred during the last ten years in Dayton, which were probably due to this disease. In November, 1926, two brothers, both butchers, were taken violently ill after having dressed rabbits for several days. One brother died three weeks after the onset of his illness; the other recovered after a stormy and prolonged convalescence. Serum of the surviving brother, taken 14 months after the onset of his illness, agglutinated *Bacterium tularensis* in relatively high titre (1:320). During Thanksgiving week, 1923, three women dressed rabbits at the C. market, in Dayton. All three became severely ill with "grippe-like" symptoms, together with axillary and epitrochlear adenitis. One of the wom-

en (Mrs. C. H.) died in two weeks. Sera of the two surviving women (Mrs. M. H., case XLI, and Mrs. W. H., case XLII) were found by Dr. Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

*Persistence of agglutinins:* Agglutinins are constantly present at sometime during the second week of the illness. An abrupt rise in the titre occurs during the third week, which reaches its maximum (1:1280 to 1:2560) in the fourth to the seventh week. During the eighth week there is usually a slight fall in titre with a gradual decline until, at the end of the first year, the average titre in one series was 1:136. There is at hand sufficient evidence to permit one to conclude that the agglutinins never entirely disappear. In one of our cases (M. T.), agglutinins were present (1:160) after 19 years and 4 months, in another instance (J. H. A.) after 15 years and 3 months (1:80), in one instance (J. C.) after 14 years and 4 months (1:320), in two other instances (R. T. and B. F.) after 11 years and 3 months (both 1:320). The final agglutinating level to which all cases seem to come is about 1:40. Questioning individuals might ask whether the annual exposure to infection while dressing rabbits might not have contributed to the persistence of the agglutinins. The evidence is against such a view because there are instances of the same persistence in laboratory workers who have not been exposed to the infection in the succeeding years after their original attack. In none of our cases of long duration mentioned above has there been any attack simulating tularemia since the

original attack, even though ten of these men have handled thousands of rabbits since that time. Several Dayton market men have stoutly declared that they have not handled rabbits since they acquired tularemia, and there is no essential difference between the agglutination titre in these individuals and that of those who have continued to handle diseased rabbits. In one laboratorian (E. F.) who has autopsied animals infected with tularemia continually since the original attack in 1919, no rise in titre has ever been noted. Moreover, in a rabbit which has been injected with a culture of *Bacterium tularensis* the height of the titre is reached about the 14th day, when the decline begins. Subsequent injections with cultures will not reverse the declining trend of that titre (27). The experience of all investigators is in accord, namely, that one attack of tularemia confers permanent immunity, that agglutinins have never entirely disappeared from any case, and that subsequent exposure to infection does not tend to elevate a *tularensis* titre acquired by the original attack.

#### DIAGNOSIS

It has been aptly said that no one can make a diagnosis of a given disease unless he has that disease in mind. The fact that all but 15 of the 613 cases which have been reported to date have been recognized during the past three years indicates that the physicians of this country have learned to recognize this disease, thanks to the writings of Francis. The onset symptoms closely simulate those of influenza and many of our cases were primarily thus diagnosed. The next most

common error has been to consider that the disease was due to streptococcus infection. A few cases simulate typhoid fever. Because of the nodular lymphangitis which has developed in some cases the diagnosis of sporotrichosis has been made. Due to the fact that the agglutinins present in the serum in tularemia will occasionally cross-agglutinate *Bacterium melitense* and *Bacterium abortum*, serologists have confused the disease with undulant (Malta) fever. It would seem that *Bacterium tularensis*, *Bacterium melitense* and *Bacterium abortum* show a serologic relationship, in the same manner that *Bacillus typhosus*, *Bacillus paratyphosus A* and *Bacillus paratyphosus B* are closely related serologically. The proportionately higher titre reached by tularemia agglutinins leaves little doubt as to the diagnosis. On the other hand, pathologists have clung tenaciously to the histopathological diagnosis of tuberculosis because of the remarkable similarity in the granulomatous lesions.

The history gives the most important clue to the diagnosis. The patient usually tells, particularly if questioned about it, of having handled wild rabbits or having been bitten by a tick or horse-fly. The primary lesion first exists as a reddish papule followed by a persistent ulcer, or as a primary conjunctivitis, usually followed by conjunctival ulcers. Almost simultaneously with the appearance of the primary lesion the persistent satellite bubo develops, and these local manifestations are accompanied by chills and fever, sweats, headache, aching sensations in the back and extremities and a feeling of great prostration.

Once the clinical diagnosis has been made it is an easy matter to confirm it. The simplest and best method is to collect 4 to 5 cubic centimeters of the patient's blood, exactly as one collects it for the Wassermann test. Either the serum or the whole blood may be sent to any laboratory which has on hand the necessary *Bacterium tularensense* antigen for agglutination reactions. The specimen may be sent directly to the Hygienic Laboratory of the United States Public Health Service at Washington, or to the state health laboratory, if it possesses the antigen. Many state health laboratories are now equipped to carry out this simple procedure. A second method is the isolation of *Bacterium tularensense* from guinea pigs inoculated with the blood of the patient or with material taken as early as the first week from the primary lesion or from the enlarged lymphnodes. Francis has repeatedly stated in his publications that all attempts to recover the organism directly from human tissues on artificial culture media have been futile. All investigators concerned with the bacteriological aspects of this disease have emphatically stated that they have been unable to recover the organism by the direct inoculation of culture media with human material derived from the primary lesion or from the regional lymphnodes. The writer succeeded in two instances (J. S. and H. C.) in growing the organism directly upon culture media from the material taken from the walls of the axillary abscesses. The organism thus recovered was passed through three series of guinea pigs. All died within a week with the characteristic

gross and microscopic tissue changes and the organism was recovered from the animal's blood and tissues and again inoculated into other animals with similar results. Furthermore, the organisms agglutinated promptly in dilutions up to 1:1280 when tested with known sera. The best growth was obtained upon cystine-glucose-peptone-meat infusion agar (Francis' medium) to which 5 per cent human serum had been added.

Cover glass preparations made directly from the pus evacuated at the time of surgical drainage are of no use in determining the identity of the organism.

*Bacterium tularensense* is a small, non-motile, Gram-negative organism, which exhibits marked pleomorphism in its growth on special culture media. It appears as a short rod and as a coccus. In a single transfer it may change from coccoid form to rod form, and in many of our cultures rods and cocci, together with transition forms, were present to the smears stained with aniline gentian violet.

#### TREATMENT

There is, as yet, no specific treatment. The treatment is entirely symptomatic. Strict confinement to bed is the most important part of the treatment. It is unwise to incise the primary lesion and it is unwise to excise, or even incise, the enlarged glands until definite suppuration is present. The most important phase of the treatment is prophylaxis, and this is best accomplished by education of market men and the laity in general as to the

dangers of the infection and the manner in which it is acquired, by urging thorough cooking to destroy the infective agent, and by the warning that all individuals who handle wild rabbits should wear rubber gloves.

In view of the fact that the agglutinins are retained permanently it seems quite logical to believe that the disease might be arrested in the acute stages by the use of immune serum, particularly that taken from individuals who have agglutinated *Bacterium tularensis* in high titre. Because of the fact that we did not know of any old cases when we undertook the present work we were unable to try this procedure this year, but we will be on the sharp lookout for acute cases during the next rabbit season and we will give this method of treatment a thorough trial.

#### THE DAYTON EXPERIENCE

##### *Fatal Case*

On the afternoon of the 25th of November, 1927, Mr. F. W., a 25-year-old colored dresser of rabbits and chickens at the J. O. F. market, of Dayton, Ohio, was admitted to the receiving ward of the Miami Valley Hospital as an emergency case. At this time he appeared as a well developed, muscular colored man, appearing to be about the stated age, acutely ill, delirious, and quite unable to give a clear account of his illness. The history was obtained from his wife.

After the onset of the present rabbit season, which, in Ohio, begins on November 15th, the patient dressed several hundred rabbits and chickens at the J. O. F. market. He developed multiple small blisters on his right

hand, more marked on the dorsum. His wife attributed these to the immersion of his hands in hot water while picking the feathers from chickens. He continued his work and felt perfectly well until one week after he first noticed these blisters. On the morning of the 22nd of November, the patient arose at the usual time, but complained bitterly of headache. However, he went to work, but about 9 o'clock in the morning he felt considerably worse and was forced to go home and take to his bed. On this day it was noticed that the glands at the right elbow and in the right armpit were swollen and tender. He remained in bed and continued to grow worse. On the morning of the 25th of November he had slight bloody expectoration. He was unable to take food; he vomited for the first time on this morning and became delirious.

In the hospital the patient was exceedingly restless, complained bitterly of pain in his head, in his back and legs, and was unable to move himself. His admission temperature was 106°F. The physical examination, except for the external findings, was essentially negative. The skin over the entire right hand from the finger tips to the wrist showed extensive exfoliation with many deep irregular fissures extending into the corium. There was no well defined ulcer. The skin of the fingers of the left hand showed a much less marked desquamation. The right epitrochlear lymph glands were moderately enlarged, the average size being that of a kidney bean. These were tender to palpation. The right axillary nodes were enlarged to the size of a small orange. These were exquisitely

painful and caused the patient to cry out whenever they were touched. Except for the decidedly septic appearance of the patient the remainder of the physical examination was essentially negative. Examination of the lungs showed slight impairment of resonance below the fourth right rib, with bronchial breathing and fine crepitant râles. Examination of the heart revealed nothing except tachycardia.

At that time it was thought that he had right lobar pneumonia with septicemia. In view of the significant occupational history, and the presence of the ascending lymphangitis and the epitrochlear and axillary adenitis it occurred to the interne, Dr. H. W. Harris, who examined the patient when admitted, that the diagnosis might be tularemia. The overwhelming character of the infection seemed to be the only argument against such a diagnosis. The writer was called in consultation and concurred in the diagnosis of tularemia. Ten cubic centimeters of blood were withdrawn at this time for guinea pig inoculation and agglutination tests. One cubic centimeter of serum was immediately injected into each of two guinea pigs. The remainder was sent to Francis, at the Hygienic Laboratory, Washington, D. C.

All attempts to reduce the patient's temperature were of no avail. On the morning of the 26th his condition was obviously worse. He became more delirious and it became necessary to employ mechanical restraint. He developed urinary and fecal incontinence, associated with a profuse watery diarrhea. His speech was thick and incoherent and he could be aroused only

with great difficulty. The temperature remained at 106°F. until 4:23 P. M. when the patient died, just 24 hours after his admission to the hospital and 4 days and 7 hours after the onset of his illness.

A blood count, made on the morning of the 25th, showed 5,200,000 red blood cells; hemoglobin, 90 per cent; white blood cells, 15,400; differential count: polymorphonuclear neutrophils 91 per cent and small lymphocytes 9 per cent.

There was some difficulty encountered in obtaining permission for post-mortem examination and it was impossible to begin the autopsy until 10:00 o'clock on the morning of November 27. The autopsy findings follow:

F. W.; age, 25; nationality, American negro; occupation, dresser of rabbits and chickens at the J. O. F. market.

Clinical Diagnosis: Pneumonia; tularemia.

#### *External Examination*

*Build:* Body is that of a slender, well developed, negro youth, appearing to be of stated age; body length, 162 cm. *General Nutrition:* Good. *Head:* Symmetrical, no scars or wounds. *Facies:* Symmetrical. *Eyes:* Pupils moderately dilated, round, equal and regular; sclerae clear. *Neck:* A few palpable kidney bean-size lymphnodes in the lower half of the anterior cervical chain. *Thorax:* Symmetrical; intercostal angle less than a right angle. *Abdomen:* Flush with the rib margin. *Back:* Well marked hypostasis over dependent dorsal areas. *Skin:* Fine, soft, relatively inelastic; deeply melanotic; the skin over the right hand from the finger tips to the wrist shows extensive exfoliation, with many deep irregular fissures extending into the corium; no well-defined ulcers; the skin of the fingers of the left hand shows a similar, but

less marked, desquamation. *Hair*: Normal distribution. *Teeth*: Carious; moderate pyorrhea. *Mucous Membranes*: Cyanotic. *Muscles*: Well developed. *Rigor Mortis*: Present over abdomen and lower extremities. *Panniculus*: Practically absent. *Edema*: None. *Body Heat*: Absent. *Mouth*: No ulcers. *Nose*: No perforation. *Ears*: No discharge. *Genitals*: No penile scars. *Anus*: No hemorrhoids or fissures.

*Spinal Cord* and *Head* not examined because of stated restrictions.

#### *Main Incision*

*Panniculus*: Represented by a few scattered lobules of fat. *Musculature*: Very well developed; the abdominal recti, especially below the umbilicus, show extensive Zenker's necrosis, presenting the typical waxy, hyaline, fish flesh-like appearance. *Abdominal Cavity*: Contains no free gas or fluid. *Omentum*: Gathered loosely about the transverse colon; no adhesions. *Position of Abdominal Organs*: Liver descends one finger's breadth below the rib margin in the midclavicular line; spleen does not descend below the rib margin. *Position of Diaphragm*: Fourth interspace on the right, fifth interspace on the left. *Costal Cartilages*: Elastic, cut with ease. *Sternum*: Abundant red-brown marrow.

#### *Thorax*

*Thoracic Cavity*: Contains no free gas or fluid. *Position of Thoracic Organs*: Normal relationship. *Anterior Mediastinum*: Lymphnodes small. *Thymus*: Replaced by thin sheet of fat; a few slender strands of persistent whitish thymic tissue. *Pericardium*: Smooth, moist and shining; multiple healed "soldiers' spots" over right ventricle; just above the apex the pericardial surfaces are firmly adherent over an area about the size of a silver dollar; sac contains about one tablespoonful of clear yellowish fluid. *Heart*: About the size of the cadaver's right fist; apex in the fifth interspace in the midclavicular line; apex formed entirely by the left ventricle; right border at right parasternal line. *Left Heart*: Wall averages 14 m.m. in thickness; no fibrosis; no in-

farcts; endocardium pale, yellowish-gray; diffuse fatty degenerative infiltration of subendocardium; marked "tiger heart"; no thromboses; mitral orifice admits two fingers; no vegetations; aortic orifice admits thumb with ease; no vegetations. *Right Heart*: Wall averages 6 m.m.; no fibrosis; no infarcts; diffuse subendocardial fatty degenerative infiltration; tricuspid orifice admits four fingers; no valvular abnormalities; pulmonic ring takes two fingers easily. *Coronary Vessels*: Thin-walled throughout. *Left Lung*: Multiple old firm pleural adhesions; a patch of healed apical tuberculosis about the size of a silver dollar; many healed subpleural tubercles; on section, marked passive congestion; moderate edema; no pneumonia; no active tuberculosis. *Right Lung*: Similar to the left except that in the lower lobe, in the costophrenic thin margin, is a walnut-size, firm, reddish-brown area which on section has the appearance of a recent abscess with a cherry-size necrotic core; in the middle lobe, just beneath the pleura, is a similar cherry-size area surrounded by a zone of purulent infiltration. *Bronchi*: Contain a moderate amount of frothy edema fluid; no purulent exudate. *Bronchial Glands*: Markedly hyperplastic and anthracotic; contain multiple healed and caseous tubercles. *Pulmonary Vessels*: Thin walled; elastic; no thrombi; no emboli. *Aorta*: Hypoplastic; thin walled; elastic; no atherosclerosis; no evidence of syphilis. *Thoracic Portion of Esophagus*: Negative.

#### *Abdomen*

*Peritoneum*: Smooth, moist, and shining throughout; no free gas or fluid. *Spleen*: About one and one-half times normal size; weight, 165 grams; measures 15x9x5 cm.; capsule smooth and shining; beneath the capsule are seen multiple whitish and grayish-white round areas varying in size from pin-head to small pea; on section, similar ones are found throughout the spleen; these do not have the appearance of hyperplastic Malpighian corpuseles or tubercles, but have more the appearance of focal necroses; pulp is rather soft over the cut surface. *Large In-*



*testine*: No ulcers; mucosa shows marked congestion. *Appendix*: In part retrocecal; arches medially toward the brim of the pelvis; no evidence of inflammation. *Small Intestine*: Marked congestion of mucosa; no ulcers; Peyer's patches small. *Duodenum*: Contains a small amount of bile-stained mucin; no ulcers or scars. *Bile Passages*: Patent. *Stomach*: Slightly distended with gas and a small amount of turbid fluid; no ulcers; no scars; mucosa congested and covered with thin layer of mucin. *Pancreas*: Normal size and consistence. *Liver*: Normal size; capsule smooth and shining; on section, shows rather marked acute congestion and cloudy swelling; no visible whitish focal necroses; no increase of stroma. *Gall Bladder*: Thin walled; mucosa intact; no sand; no calculi. *Portal Vein*: No thrombosis. *Mesenteric Lymphnodes*: Slightly enlarged; no caseous necrosis. *Left Adrenal*: Moderately hypoplastic, particularly in the medulary portion. *Left Kidney and Ureter*: Normal size; capsule strips readily, leaving a smooth congested surface; on section, marked cloudy swelling and passive congestion; pelvis, thin walled; ureter, negative. *Right Adrenal*: Similar to the left. *Right Kidney and Ureter*: Similar to the left. *Abdominal Aorta*: Thin walled; hypoplastic; no atherosclerosis; no evidence of syphilis.

#### *Male Pelvis*

*Penis*: No scars. *Scrotum*: No edema. *Testis*: Soft; no evidence of orchitis fibrosa syphilitica. *Rectum*: Marked passive congestion. *Prostate*: Normal size and consistence; no glandular hyperplasia. *Seminal Vesicles*: Thin walled; moderately distended with seminal fluid. *Urethra*: Negative. *Bladder*: Greatly distended with urine; fundus four fingers' breadth above the symphysis pubis; mucosa shows congestion of trigon.

#### *Special Regional Examination*

*Lymph Glands*: The right epitrochlear lymph glands are moderately enlarged, averaging kidney-bean size. The right axillary nodes are tremendously enlarged, many of them being of plum size. On section, these

nodes are very soft, friable, and show extensive caseation.

#### *Microscopic Findings*

*Axillary and epitrochlear lymphnodes*: Multiple focal necroses, miliary and submiliary in size. The necrosis is very recent. The nuclei of the necrotic lymphocytes show karyoschisis and karyorrhexis. Early caseation necrosis. The periphery of the necrotic areas is irregular, but very sharply defined from the neighboring intact lymphocytes. Surrounding these focal necroses there is early fibroblastic and epithelioid proliferation, with marked hyperplasia of the reticulo-endotheliocytes. The epithelioid granulation tissue is devoid of new formed capillaries. The process has been too acute for the development of mature connective tissue. No distinct foreign-body giant cells of the Langhans type are to be seen, although some of the histiocytes have fused to form a kind of symplasm, probably representing early giant cell forms. Alcohol-fixed paraffin sections show no tubercle bacilli by the modified Ziehl-Neelsen method as applied to tissue sections. Smears made from the lymphnodes before fixation showed no acid-fast organisms. A few scattered polymorphonuclear leucocytes at the periphery of the foci of necrosis. Practically no distinct germ centers. The capillaries are widely dilated and engorged with red blood cells. (See Fig. 2.)

*Heart*: Diffuse subendocardial fatty degenerative infiltration. "Tiger heart." Healed epicarditis.

*Lungs*: Extreme acute passive congestion, with moderate edema. In the right lung are two areas of caseous necrosis with polymorphonuclear infiltration at the periphery. These suggest tularemic necroses. Healed tubercles. Chronic adhesive pleuritis.

*Bronchial lymphnodes*: Multiple healed tubercles.

*Spleen*: Multiple focal necroses, varying in size from pin-point to small pea. The lesions are essentially similar to those found in the axillary nodes. In some low-power fields, eight to ten small foci of necrosis can be gathered into one field. The necroses

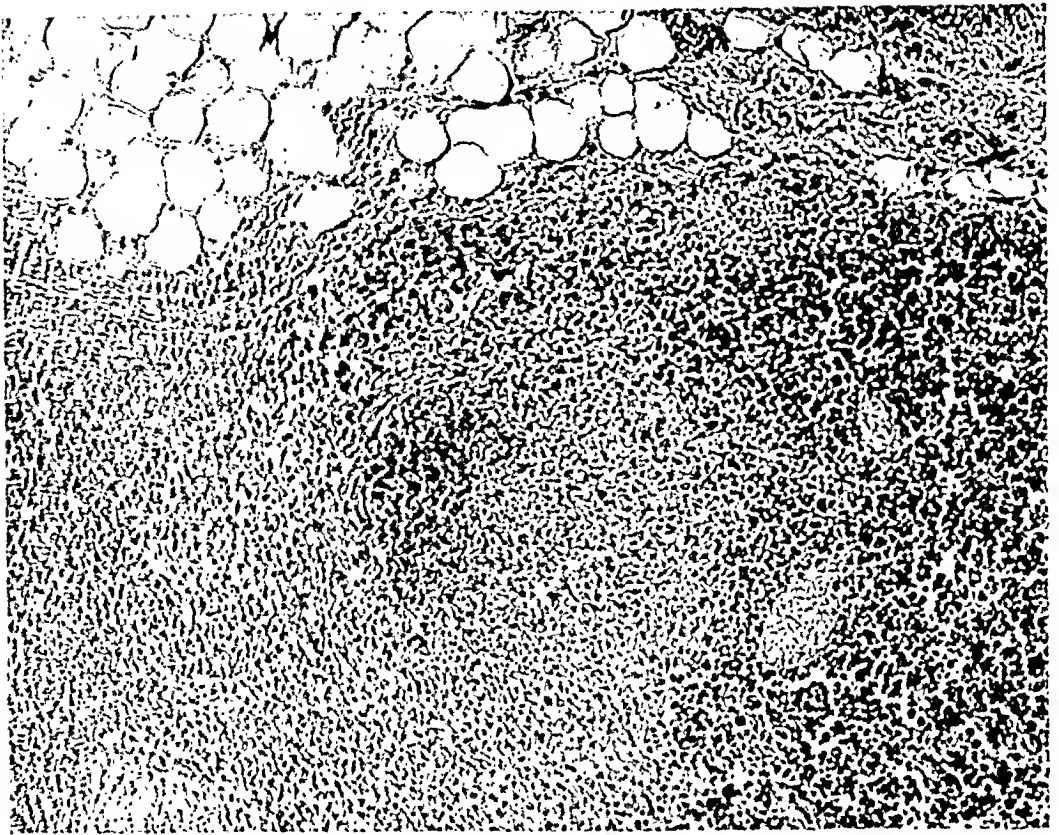


FIG. 2. Mr. F. W. died on fourth day of disease. Photomicrograph of periphery of axillary lymph node, showing focal necrosis, with early fibroblastic and epithelioid proliferation and hyperplasia of reticulo-endotheliocytes. Intact lymphocytes at right. Perilymphadenitis, involving surrounding axillary fat. No Langhans' giant cells.

involve by far the greater part of practically every low-power field. Malpighian corpuscles show a decided diminution in number of lymphocytes. Intense acute passive congestion. Some of the focal necroses are surrounded by a zone of fibroblastic and epithelioid cells, while others show little or no peripheral reaction. No mature Langhans' giant cell forms. Marked diffuse reticulo-endothelial hyperplasia. (See Fig. 3.)

*Liver:* A few submiliary focal lesions with rather extensive reticulo-endothelial proliferation. Very little caseation necrosis. Marked cloudy swelling and localized areas of simple necrosis. (See Figs. 4 and 5.)

*Stomach:* Excessive mucin.

*Kidneys:* Very marked cloudy swelling and localized simple necrosis, involving chiefly the proximal convoluted tubules. Mul-

tiple hyaline casts in collecting tubules. Marked acute passive congestion. No focal necroses. (See Fig. 6.)

*Adrenals:* Hypoplasia of medulla. Lipoidosis of cortex. No focal necroses.

*Striped Muscle (rectus abdominis):* Marked Zenker's necrosis. Large hyalinized fibers, with very few intact nuclei. Marked difference in eosinophilic staining qualities. Fragmentation of myofibrils. Cohnheim's areas indistinct. Typical intracellular coagulation necrosis. (See Fig. 7.)

#### PATHOLOGICAL DIAGNOSIS\*

##### *Tularemia. Exfoliating dermatitis of*

\*A more complete pathological study of the early lesions of tularemia in the lymph-nodes and viscera will appear in the Archives of Pathology.

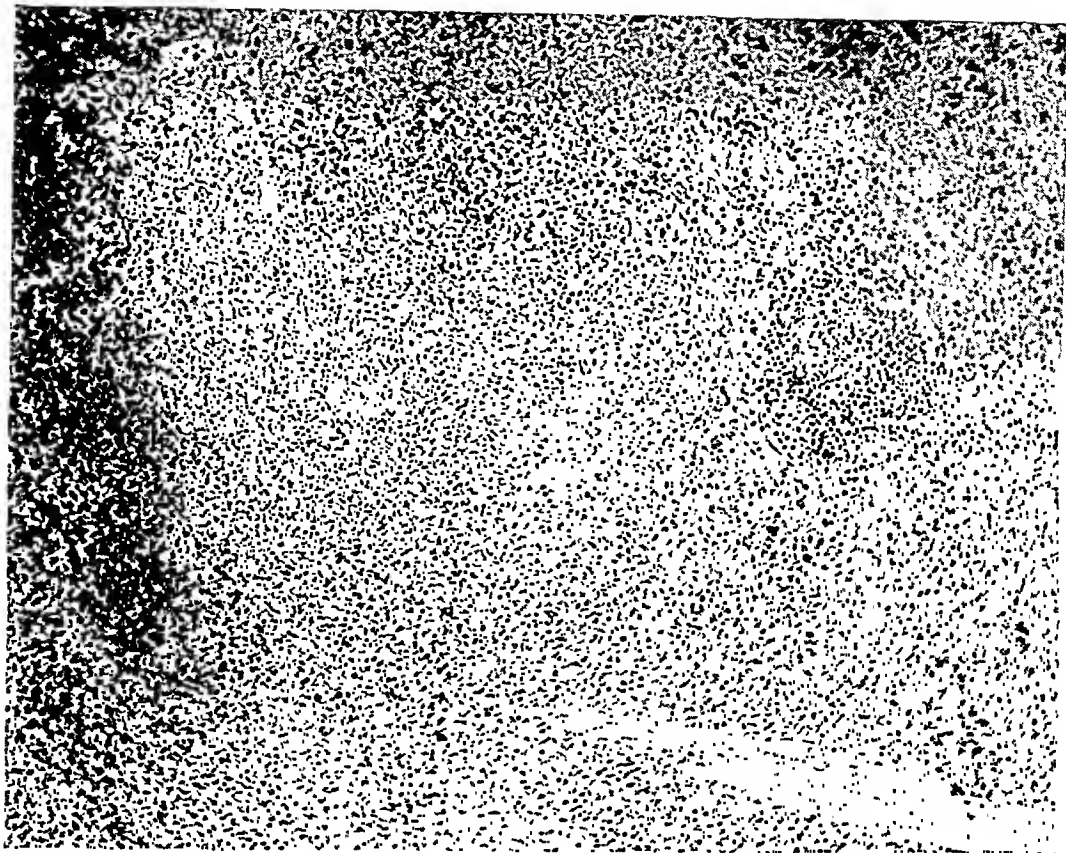


FIG. 3. Mr. F. W. Photomicrograph of spleen, showing multiple foci of necrosis, with early epithelioid and fibroblastic proliferation, and marked reticulo-endothelial proliferation. Marked diminution of lymphocytes in Malpighian corpuscles. No Langhans' giant cells.

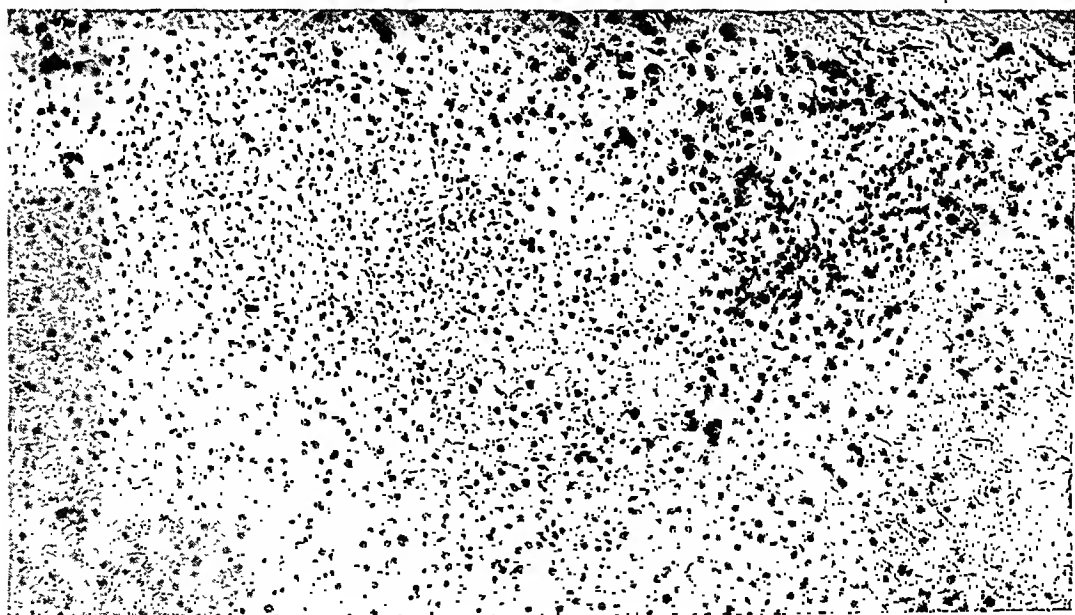


FIG. 4. Mr. F. W. Photomicrograph of two early tularemic lesions in liver. Practically no necrosis, but a marked hyperplasia of reticulo-endothelium. Cloudy swelling of hepatic parenchyma.

*hands, most marked on right. Ascending lymphangitis of right upper extremity, with epitrochlear and axillary lymphadenitis. Multiple focal necroses of epitrochlear and axillary nodes, spleen, liver, and right lung. Marked cloudy swelling and localized simple*

This case is by all odds the most rapidly fatal case of tularemia on record (four days, seven hours). Furthermore, the case is unusual in that there is no doubt that tularemia *per se* was the cause of death. In the other fatal cases, of which 23 have

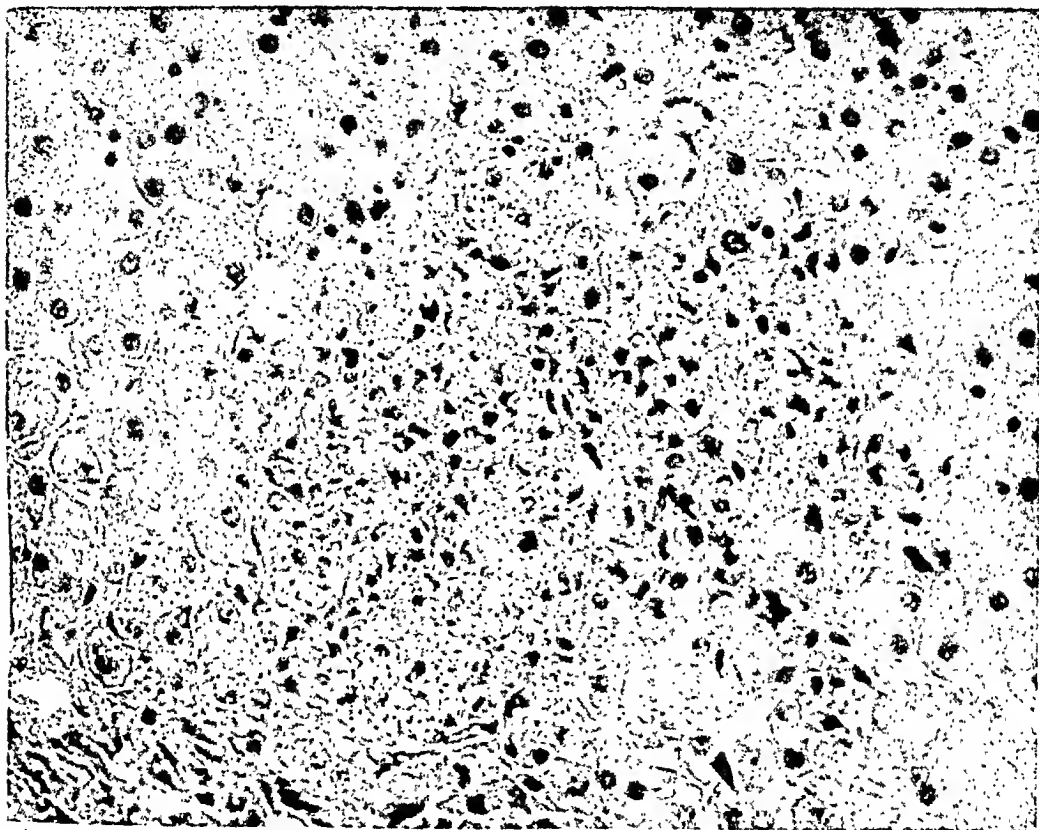


FIG. 5. Mr. F. W. High power photomicrograph of early tularemic lesion of liver, showing marked reticuloendothelial hyperplasia.

*necrosis of liver and kidneys. Subendocardial fatty degenerative infiltration. Healed tuberculosis of lungs and bronchial nodes. Terminal right sided cardiac dilatation with relative tricuspid and pulmonary insufficiency. Pulmonary congestion and edema. Old adhesive pleuritis and pericarditis. Marked Zenker's necrosis of recti abdominis.*

been reported, there was usually some contributing factor, such as pneumonia, streptococcus septicemia or heart disease.

Immediately after the autopsy, two healthy guinea pigs were inoculated with axillary lymphnode tissue, which had been rubbed up in a mortar, suspended in physiological saline solution, and strained through coarse gauze.

On November 30, the following telegram was received. "Serum negative for tularemia because taken too early in disease. You should exclude tuberculosis. Letter follows. Francis, Hygienic Laboratory."

four of the culture tubes the medium was enriched with 5% human serum. Tubes of nutrient agar and broth were likewise inoculated. The remaining pig died during the night of November 30 and December 1 and the same pro-



FIG. 6. Mr. F. W. Photomicrograph of cortex of kidney showing cloudy swelling and simple necrosis of the epithelial lining of the proximal convoluted tubules. The nuclei of the epithelium of the distal convoluted tubules are intact. The lumina of many of the distal convoluted and straight tubules contain hyaline tubular casts.

One hour after this telegram was received the first of the two guinea pigs, inoculated with the patient's serum on the afternoon of November 25, died and was autopsied immediately. The characteristic spotted spleen and liver was found, and the heart's blood was placed upon cystine-glucose-peptone-meat infusion agar. In

cedures were carried out. Both of the animals inoculated with axillary lymphnode tissue, immediately after the necropsy of F. W., died in four days, with the characteristic gray, granular caseation of the enlarged lymphnodes of the groin, and great numbers of small whitish foci of necrosis in the spleen and liver.

The negative report from Dr. Francis was anticipated, in view of the fact that the blood had been taken on the third day of illness and in the presence of an overwhelming bacteremia. Agglutinins have never been demonstrated in the first week of tularemia.

particularly since the young man had worked in a wholesale market which had distributed 12,000 rabbits to the markets of the city during the preceding week. It was learned that the rabbits purchased by the company for which F. W. worked had been procur-

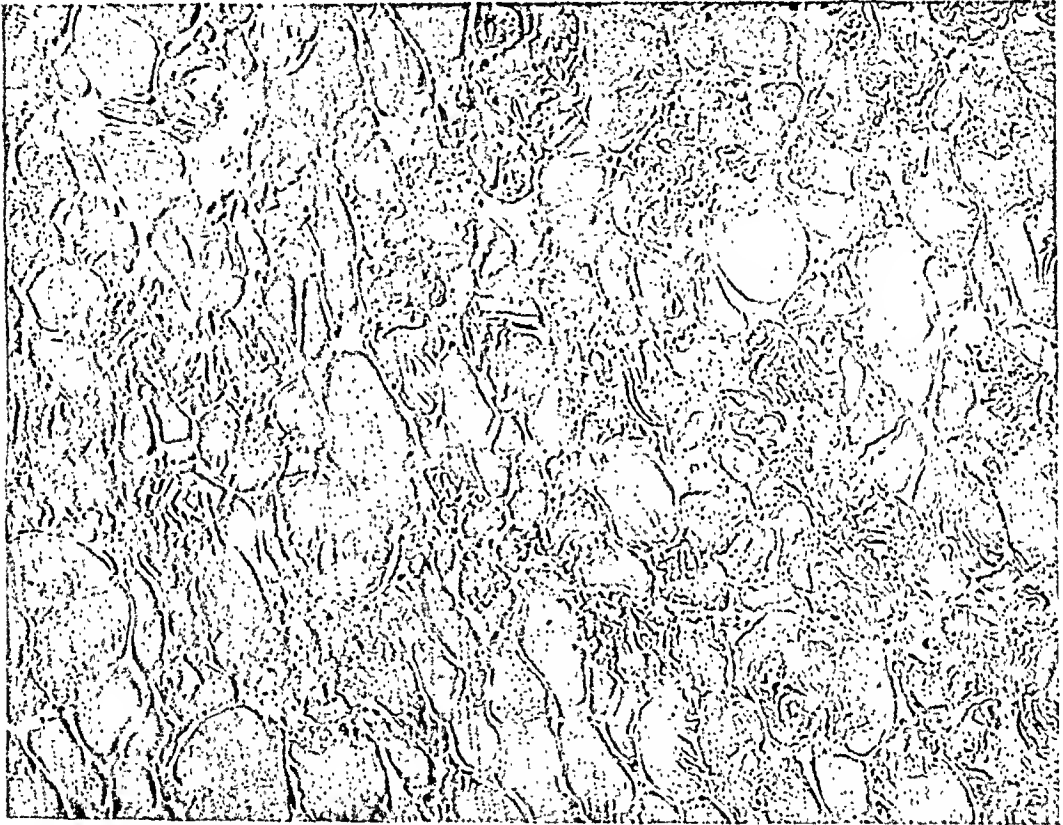


FIG. 7. Mr. F. W. Photomicrograph of voluntary muscle of rectus abdominis, showing intracellular hyaline or coagulation necrosis of fibers and absence of nuclei. Typical Zenker's necrosis.

The writer was invited to give a discussion on tularemia before the Montgomery County (Ohio) Medical Society, on Friday evening, December 2. The findings in the fatal case were given, together with an historical sketch of the disease, and it was pointed out that in view of the occurrence of this fatality from tularemia there must be other cases in the city, par-

ed at Maysville and Cynthiana, Kentucky. There is a state law which prohibits the sale of rabbits killed in Ohio. Consequently most of the rabbits sold in this State during the rabbit season are shipped from Kentucky.

On the day following this discussion, six cases were reported to the writer, all of which were proved to be tularemia.



All of the cystine agar cultures, made on November 30, showed the first growth of the characteristic grayish-white small circular colonies on December 3. There was no growth on the nutrient agar medium or in broth. The culture on the cystine agar enriched with human serum was more luxuriant than that on the cystine-glucose-meat infusion-peptone agar. Sterile salt solution suspensions of the organism were injected into three healthy guinea pigs. The guinea pigs thus inoculated died in four days with the characteristic tularemic lesions, and the organism was again recovered from the heart's blood and splenic tissue. Similar animal inoculations were carried out with the material from the remaining guinea pigs originally inoculated, with the same result. The organism was then passed through four series of animals. In each instance the cultures recovered from the animals were taken off in two-tenths per cent formalin and used as an antigen for agglutination against known anti-*tularensis* serum. In each instance the organisms agglutinated out promptly to the full titre of the serum.

The hair was shaven from the abdomen of four guinea pigs and the abraded skin was rubbed lightly with pieces of spleen from animals recently dead of tularemia. All of the animals thus treated developed the disease and died within four or five days. The autopsy showed the characteristic gross lesions and in each instance the organism was recovered from the dead animals. Splenic tissue was then rubbed lightly on the unshaven, unabraded, intact skin of the abdomen of four guinea pigs. Two of the animals died,

one on the fifth day and one on the sixth day, with the characteristic gross lesions; from both the organism was recovering, thus demonstrating that the organism will penetrate unbroken skin.

Tiny fragments of splenic tissue taken from animals recently dead of tularemia were placed in the right conjunctival sac of two healthy guinea pigs. Both animals showed excessive lacrimation on the following day. On the third day there was a grayish-white thin film over the entire conjunctival surface, with marked capillary injection and multiple minute ulcers. Both animals died on the fifth day, with characteristic visceral lesions and caseous regional lymphnodes.

Spleens from the autopsied animals were dropped into tubes containing sterile glycerine and placed in the ice box. Two months after they had been first placed in the ice box, two of the spleens were ground up in a mortar, suspended in physiologic saline solution, and strained through gauze. Two animals were inoculated with the material and both developed the disease, thus demonstrating the extraordinary resistance of this organism.

In view of the large number of infections with *Bacterium tularensis* among laboratory workers the greatest caution was exercised throughout all of the experimental work. The animals were immersed in ten per cent formalin solution before autopsy. Sterile gowns, sterile gloves, masks and glasses were worn. All tissues were handled with sterile instruments. All materials used were sterilized immediately after the autopsy and the benches on which the work had been carried out were wash-

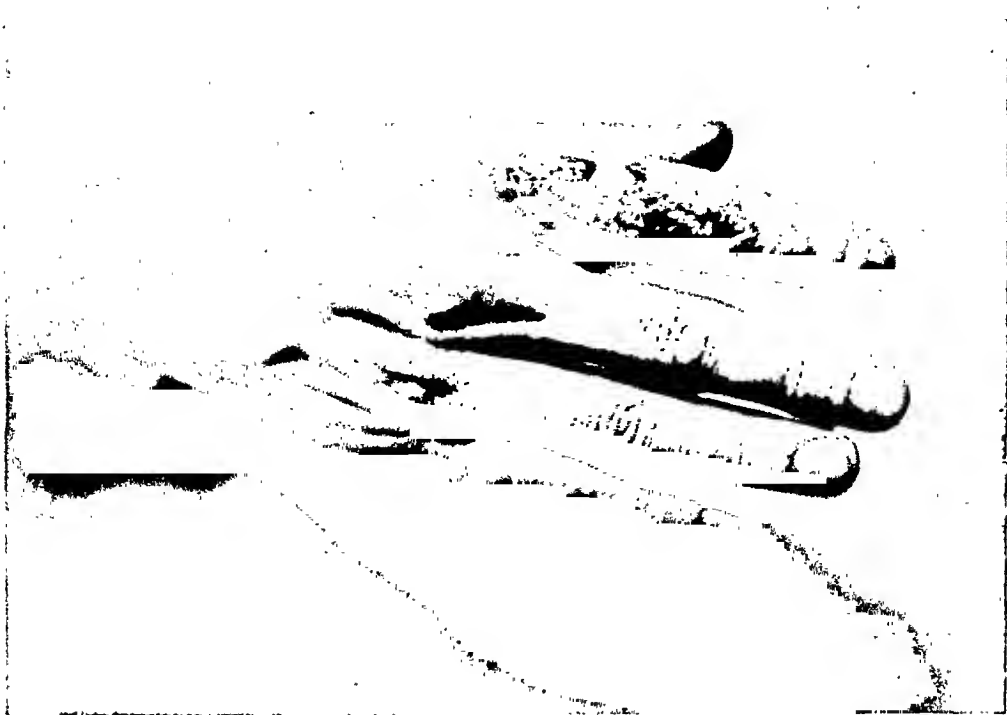


FIG. 8. Mr. H. C., case XIX. Primary lesion of right index finger, overlying proximal interphalangeal articulation, after incision. Nodular lymphangitis overlying metacarpophalangeal articulation. Photograph taken 6 weeks after onset.



FIG. 9. Mr. H. C., case XIX. Axillary adenopathy and sporotrichosis-like nodular lymphangitis of upper arm. Six weeks after onset.



ed off with ten per cent formalin solution. The hands were washed with soap and water, then immersed in ten cent formalin solution for a few moments and then held under running water. The cages in which the animals died were immersed in boiling water. No person engaged in the experimental work in our laboratory contracted the disease.

On December 13 the following letter was received:

TREASURY DEPARTMENT  
UNITED STATES PUBLIC HEALTH  
SERVICE  
WASHINGTON, D. C.

December 12, 1927

Hygienic Laboratory  
Twenty-Fifth and E. Streets NW.

Dr. W. M. Simpson, Pathologist,  
Miami Valley Hospital,  
Dayton, Ohio.

Dear Doctor Simpson:

Serum of Felton Williams, on which I reported negative agglutination November 30th was injected November 29th subcutaneously into pig No. 1 and intraperitoneally into pig No. 2. Pig No. 1 was killed while dying December 5th and showed the typical lesions of tularemia—caseous lymph nodes and spotted spleen and liver. Pig No. 2 died December 2nd, showing no gross lesions of lymph nodes, but showed the spotted spleen and liver.

Cultures of heart blood of pig No. 2, taken at moment of death, showed growth December 4th from which a transfer was made December 5th. The latter was taken off in 0.2% formalin and used December 11th as an antigen for agglutination against a known anti-tularensis serum, a known tularensis organism being also set up in the agglutination test. Both organisms agglutinated out promptly to the full (1:1280) titre of the serum.

Transfers from the spleen of pig No. 2, to the shaven abraded skin of the abdomen

of two pigs caused their death December 6th and they showed the typical lesions of tularemia—caseous lymph nodes and spotted spleen and liver.

Your case is the most rapidly fatal (5 days) of any on record. The next shortest are the family group which died in Virginia on the 6th, 8th and 8th days, respectively; the next is the case which died August 9, 1927, at St. Mary's Hospital, Duluth, Minnesota, on the 13th day; the next is the case which died December 8, 1927, on the 14th day, at the United States Naval Hospital, Washington, D. C.

I admire the way you have attacked the situation, but I must warn you that if you continue to autopsy infected pigs you are sure to go to the hospital—there have been 20 laboratory infections of man in 5 laboratories in this country, in England and in Japan.

Sincerely yours,  
Edward Francis, Surgeon.

#### NON-FATAL CASES

##### A. 1927 CASES

When the cause of death in the case of F. W. was established, our attention was directed to the other rabbit dressers at the J. O. F. market. It soon developed that eight other rabbit handlers at this market were acutely ill. All of the rabbits dressed at this market had been received from Maysville and Cynthiana, Kentucky. Rabbits shipped to Dayton from Kentucky, Missouri and Kansas have been responsible for all but five of our cases. In these five instances, the disease resulted from contact with rabbits killed in the woods near Dayton. Within the next two months the writer saw 24 persons who were suffering from the disease. All of the persons involved in the 1927 epidemic developed the disease during November. In no case did the disease result from contact with domestic rabbits. This is

in keeping with the experience of other investigators.

#### Case I

Mr. W. S., age 49, dressed rabbits at the J. O. F. market on November 24, 1927. He had previously dressed chickens and had acquired several fissures in the skin of both hands as a result of constant immersion in hot water. On November 26, he was taken suddenly ill with chills, severe headache and throbbing pain in the left hand. At the same time he noticed a painful mass in the left axilla which rapidly reached the size of a lemon. His fever reached 103°F. and he was delirious for one week. He was confined in bed for 16 days. The axillary mass was incised and drained. It was 12 weeks from the time of the onset of his illness before Mr. S. was able to return to his work. He still complains (February 29) of great weakness.

Serum of Mr. S., taken on December 9, 1927, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:160.

#### Case II

Mr. L. H. F., age 43, dressed rabbits at the J. O. F. market on the day before Thanksgiving, 1927. He perforated the skin of the pad of the right thumb with a sharp needle-like fragment of rabbit spine. One drop of blood escaped after the perforation. On the Saturday after Thanksgiving, he experienced chills, a fever which went to 101°F. and he noticed for the first time a painful swelling in the right axilla which assumed the size of a small lemon. At the same time he noticed an English walnut size mass in the left axilla, with ascending reddish streaks on both arms. Shortly after this he noticed a small papule at the point of injury to his thumb which rapidly developed into a dime-size ulcer. The primary lesion was incised on the following day. Mr. F. remained in bed for four weeks. The axillary mass was not incised nor did it drain spontaneously. Mr. F. was unable to return to his work until February 3, 1928. He still feels very weak.

Serum of Mr. F., submitted to Francis on

December 18, 1927, was found to agglutinate *Bacterium tularensis* in all dilutions to 1:640.

#### Case III

Mr. E. B., age 43, had dressed rabbits and chickens at the J. O. F. market since the beginning of the rabbit season, November 15, 1927. While dressing chickens he had immersed his hands for long periods in hot water and had acquired several small fissures. On November 30, 1927, he developed chills and fever and a severe headache. Even though his doctor, Clement Fischer, insisted that he go to bed he refused to do so for any length of time. The right axillary mass assumed the size of a lemon. After it became fluctuant it was incised. Mr. B. returned to his work on January 9, 1928, still feeling very weak.

Serum of Mr. B., collected on December 17, 1927, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:160.

#### Case IV

Mrs. D. S., age 45, patient of Dr. Clement Fischer, dressed rabbits at the J. O. F. market. On November 25, she perforated the little finger of the left hand with a sharp fragment of rabbit bone. Three days later she was taken suddenly ill with a severe chill and a rapid elevation of temperature to 103°F. She suffered severe headache and aching pains in the extremities and back. A walnut size mass appeared in the left axilla. She was confined to bed at St. Elizabeth's hospital for six weeks. She returned to her home where she was forced to lie down most of the time, quite unable to do any work. On February 25, 1928, she was readmitted to St. Elizabeth's hospital for the surgical drainage of a left axillary abscess which had extended beneath the pectoralis major muscle. She was confined to bed at this time for three weeks. She is still very weak and unable to do the duties to which she is accustomed.

Serum of Mrs. S., taken on December 18, 1927, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:160.

TABLE I  
1927 Cases

Case No.	Initials	Sex	Age	Occupation	Source of Infection	Primary Lesion	Incubation Period	Onset Date	Adenopathy	Suppuration	Agglutination (by Francis)	Convalescence	Type
1	F.W.	M	25	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Multiple fissures of right hand. No ulcer.	Unknown	Nov. 22, 1927	Right epitrochlear and axillary	None	Proved by animal inoculation	Died, 40 days after onset	0
2	W.S.	M	49	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Multiple fissures	2 days	Nov. 26, 1927	Left axillary	Incised	1:160	Twelve weeks plus	0
3	L.H.	M	43	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Right thumb	3 days	Nov. 23, 1927	Right and left axillary	None	1:640	Four weeks plus	UG
4	E.B.	M	43	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Multiple fissures	Unknown	Nov. 30, 1927	Right axillary	Incision	1:160	Five weeks plus	0
5	D.S.	F	45	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left little finger	3 days	Nov. 25, 1927	Left axillary	Incised	1:320; partial 1:640	Four months plus	UG
6	R.H.	M	23	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	No ulcer	3 days	Nov. 25, 1927	Left axillary. Nodular lymphangitis.	Incised	1:640; partial 1:1280	Two months	3
7	A.A.S.	F	40	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left middle finger	2 days	Nov. 23, 1927	Left epitrochlear and axillary. Nodular lymphangitis	None	Tularensis, 1:1280 Abortus, 1:320 Melitensis, 1:320	Two months	UG
8	O.E.	M	42	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left index finger	2 days	Nov. 24, 1927	Left axillary. Nodular lymphadenitis.	Incision	1:1280	Four weeks	UG
9	C.A.	M	20	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left thumb	Indefinite	Nov. 23, 1927	Left axillary, right epitrochlear	Incision of right epitrochlear ear mass	1:640	Three months plus	UG
10	J.K.	M	40	Meat cutter	Kentucky rabbits	Palmar surface of right hand	3 days	Nov. 23, 1927	Right epitrochlear and axillary	None	1:640	Two months plus	UG
11	T.P.E.J.	M	52	Realtor	Kentucky rabbit	Left ring finger	6 days	Nov. 27, 1927	Left axillary. Nodular lymphangitis.	None	1:640; partial 1:1280 Abortus, 1:40	Eight weeks	UG
12	A.B.	F	30	Housewife	Local rabbit	Right thumb	Seven days	Nov. 26, 1927	Right axillary	None	1:160		UG
13	A.K.	M	20	Meat cutter	Kentucky rabbits	Right thumb	2-6 days	Nov. 26, 1927	Right axillary	Incision	1:2560	Three weeks	UG
14	C.H.	F	36	Housewife	Local rabbit	Right middle finger	Two days	Nov. 25, 1927	Right axillary and epitrochlear	Incision	1:1280		UG
15	I.S.	F	50	Housewife	Kentucky rabbit	Right thumb	Two days	Nov. 24, 1927	Right epitrochlear and axillary	None	1:2560	Four months plus	UG
16	J.S.	M	38	Commission merchant	Kentucky rabbits	Left index finger. Right thumb	Four days	Nov. 26, 1927	Left epitrochlear and axillary. Right epitrochlear and axillary.	Excision	1:2560	Five months plus	UG
17	D.C.H.	M	22	Farmer	Kentucky rabbits	Web between right thumb and index finger	Four days	Nov. 26, 1927	Right axillary	Spontaneous	1:1280	Six weeks	UG
18	BLANK	M	65	Farmer	Kentucky rabbits	Fourth finger right hand	Four days	Nov. 26, 1927	Right axillary	None	1:1280	Six weeks	UG
19	F.C.	M	40	Farmer	Kentucky rabbits	Fourth finger right hand	Four days	Nov. 26, 1927	Right epitrochlear. No axillary.	None	Tularensis, 1:640 Abortus, 1:80 Melitensis, 1:80	Four weeks	UG
20	R.C.	M	20	Poultry and rabbit dresser	Kentucky rabbits	Index finger right hand	Four days	Nov. 25, 1927	Right axillary. Nodular lymphangitis.	Excision	1:1280	6 months plus	UG
21	G.P.	M	25	Poultry and rabbit dresser	Kentucky rabbits	Right thumb	Four days	Nov. 21, 1927	Right axillary	None	1:320	Rapid	UG
22	A.L.G.	M	34	Orocer	Kentucky rabbit	Right middle finger	Two days	Nov. 20, 1927	Right axillary	Excision	1:1280	6 months plus	UG
23	TEAM	M	67	Retired farmer	Local rabbits	Web between left thumb and index finger; also left right finger.	Two days	Nov. 18, 1927	Left axillary	None	1:160	Two months	UG
24	EAS	F	42	Housewife	Kentucky rabbit	Right thumb	Two days	Nov. 30, 1927	Right epitrochlear. No axillary	None	1:1640	4 weeks plus	UG

G = Glandular type

UG = Ulceroglandular type

## Case I'

Mr. H. H., age 21, dressed rabbits at the J. O. F. market on November 22, 1927. Three days later he was taken suddenly ill with chills, high fever, and large painful glands in the left axilla. The index finger of the left hand was swollen but there was no ulcer. Dr. Clement Fischer made the diagnosis of glandular type of tularemia. Just above the bend of the elbow in the inner bicipital groove a walnut size nodule developed. This nodule was later incised by Dr. Fischer. The axillary mass did not break through the skin nor was it surgically drained. Mr. H. remained in bed for two weeks and was unable to return to his work for two months.

Serum of Mr. H. taken on December 17, 1927, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:640 with partial agglutination at 1:1280.

## Case VI.

Mrs. A. A. B., age 40; helper at J. O. F. market; patient of Dr. Clement Fischer. On Friday night, November 18, and on Monday night, November 21, 1927, Mrs. B. dressed rabbits. On Monday evening she stuck the sharp edge of a rabbit bone into the lateral aspect of the distal phalanx of the dorsal surface of the middle finger of the left hand, near the finger nail. The next day there developed a "run around" (paronychia). On Wednesday evening she experienced a severe chill followed by a drenching sweat, and accompanied by high fever and severe aching pains all over the body. At this time she noticed a dozen small nodules along the lymphatics of the forearm, with a walnut size nodule over the inner aspect of the biceps at the junction of the proximal and middle thirds of the arm. Two small cherry sized left epitrochlear swellings developed, together with a hen's egg size mass in the left axilla. Two days later (November 25) she was admitted to St. Elizabeth's hospital with an admission temperature of 105°F. She was delirious from the time of the onset of her illness, on Wednesday, until the following Sunday. On Monday, November 28, the

finger lesion was lanced by a physician. The chills, sweats, fever and prostration continued during her nine days' stay in the hospital. After she returned to her home she was compelled to lie down most of the time for three weeks. Since that time she has been very weak and unable to do her accustomed amount of work. The axillary mass was not surgically incised nor did it rupture spontaneously. When examined by the writer on February 27, 1928, a walnut size firm mass was present in the axilla and several small firm nodules along the lymphatics of the forearm and one cherry size firm nodule in the arm.

Serum of Mrs. B., taken on December 17, 1927, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:1280, *Bacterium abortus* in all dilutions to 1:320, and *Bacterium melitense* in all dilutions to 1:320. A second specimen, taken January 10, 1928, agglutinated these three organisms in the same titre as previously found. A third specimen, collected on February 27, 1928, agglutinated *Bacterium tularensis* in all dilutions to 1:640.

## Case VII

Mr. O. E. F., age 42; poultry and rabbit dresser at the J. O. F. market. On the 20th of November, 1927, Mr. F. scratched the skin of his left index finger over the medial aspect of the distal phalanx with a piece of ice. Two days later he dressed rabbits. On Thanksgiving day, two days after dressing the rabbits, he experienced an excruciatingly severe headache, accompanied by chills and fever. In the middle of the flexor surface of the left forearm a hickory nut size mass developed on Thanksgiving day. The next day he first noticed a similar mass over the inner aspect of the left arm in the groove between the biceps and triceps. These became exquisitely painful, and the one in the arm was lanced by a physician. When seen by the writer on February 8, 1928, the nodule in the mid-forearm was about the size of a hickory nut and covered by very thin skin, and looked to be on the point of spontaneous rupture. At no time did Mr. F. suffer from any

axillary pain, although he complained of some difficulty in elevating the arm above the level of the shoulder. On deep palpation a cherry-size firm node was found in the left axilla. Mr. F. took to his bed on Thanksgiving day and remained there for four weeks, during which time he lost 28 pounds. He is quite active now, although he complains that he does not feel as well as he did before the onset of this illness.

Francis reported that the serum taken on February 8, 1928, from Mr. F., agglutinated *Bacterium tularensis* in all dilutions to 1:1280.

#### Case VIII

Mr. C. A., age 20; poultry and rabbit dresser at the J. O. F. market. Mr. A. dressed rabbits for ten days before Thanksgiving, 1927. He had an old, unhealed knife-cut on the left thumb just above the nail. The day before Thanksgiving he became acutely ill with a high fever (104.5°F.). He suffered from severe headache, pains in the back and extremities, chills and sweats. On Thanksgiving day he noticed for the first time a painful swelling in the left axilla which, during the next week, assumed the size of a lemon. At the same time that the left axillary mass developed a similar mass appeared in the right epitrochlear nodes which rapidly assumed the size of a hen's egg. He applied flax seed poultices to both masses. The right epitrochlear mass was drained surgically, 14 days after the onset of his illness. The left axillary mass "came to a head and broke." A small ulcer developed at the site of the old knife cut. He remained in bed for fifteen days during which time the fever persisted. To date, February 26, he has been unable to return to his work because of extreme weakness.

Serum of Mr. A., collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularensis* in a dilution of 1:640.

#### Case IX

Mr. J. K., age 40, a butcher at the S. market scratched his hands in many places while dressing rabbits three days before Thanksgiving, 1927. These rabbits had been

received from Kentucky. On the day after Thanksgiving his hand became swollen and there developed distinct reddish-blue streaks along the lymphatics of the right upper extremity and he very rapidly developed large and very painful lymphnodes in the axilla and in the epitrochlear area. Several of the epitrochlear nodes were of kidney bean size while the axillary mass was the size of an English walnut. He developed a fever of 103.5°F., together with a moderate leucocytosis (12000). In the center of the right palm the writer found a reddish papule, 1 cm. in diameter. This had been incised by a family doctor on the day after Thanksgiving; no purulent exudate escaped, and the patient felt worse after the incision. This was the first case to be recognized clinically in Dayton after the fatal case. The correct diagnosis was made by Dr. E. E. Bohlender.

A blood specimen, collected on December 2, was found to agglutinate *Bacterium tularensis* in dilutions of 1:2, 1:5, and 1:10. This was in accord with the results anticipated with a serum collected on the ninth day of illness. An attempt was made one week later to obtain a second specimen but it was found that the patient had disappeared from the city. He was located in Cincinnati, on February 28, 1928. Serum collected on this date was found by Francis to be positive in all dilutions to 1:640.

#### Case X

Mr. P. S. J., age 52; real estate salesman; patient of Dr. H. F. Koppe. Mr. J. purchased a rabbit in the Arcade market on November 21, 1927. It had already been skinned and dressed. The only contact with the rabbit occurred while Mr. J. was cutting the rabbit into small pieces preparatory to cooking. He did not cut or scratch himself during the process. On November 27 he had a rather severe chill and felt that he was acquiring "grippe." The chill was followed by an elevation of temperature, and Dr. Koppe was called. He found the temperature to be 103°F., pulse 120. The patient complained of chilly sensations and of generalized aching pains all over, but espe-

cially marked in the back of the neck. The patient felt certain that he had the "grippe." On physical examination, there was a small reddened area adjacent to the nail on the ring finger of the left hand. This had the appearance of an infected hang nail. There was slight enlargement of the left axillary lymphnodes. Over the abdomen, thighs and scrotum was a maculo-papular eruption. On December 3 the patient was able to come to Dr. Koppe's office, where it was found that the axillary mass had reached lemon size and that the lymphatics in the internal bicipital furrow were reddened and indurated, with two nodular swellings just above the inner condyle of the humerus. Weakness was the most marked symptom. During this period the temperature fluctuated from 98° to 101°. On December 15 blood was taken to confirm the clinical diagnosis of tularemia.

Francis found that the serum agglutinated *Bacterium tularense* in all dilutions to 1:320, but not in higher dilutions. On December 19, a second specimen was sent which agglutinated *Bacterium tularense* in all dilutions to 1:640, with partial agglutination at 1:1280. The later specimen also cross-agglutinated *Bacterium abortum* (1:40). The patient remained in bed until December 21 when he returned to his work, still feeling very weak. There has been little diminution in the size of the axillary mass or in the nodules along the lymphatics of the arm but they are not painful and show no signs of rupture (see photographs).

#### Case XI

Mrs. A. B., age 50; housewife; patient of Dr. V. E. Hutchens. Mrs. B. prepared a rabbit for cooking at her home. The rabbit had been killed on November 19th, 1927, in the woods of Adams County, Ohio. Soon after preparing the rabbit Mrs. B. noticed an abrasion upon her right thumb. This remained slightly sore for about seven days when the thumb became greatly swollen and extremely painful. At this time she experienced slight chills. Dr. Hutchens was called on the ninth day of her illness, when he found a temperature of 100°F. and the

pulse of 108. There was a large papule on the right thumb, and the right axillary nodes were enlarged to the size of a large cherry and were very tender; there were no palpable epitrochlears. The patient states that her fever commenced seven days after the injury to her thumb. The center of the papule broke down, the central necrotic core sloughed out, leaving an ulcer  $\frac{1}{4}$  inch in diameter with a deep necrotic base. The axillary glands have, to date, shown no tendency to suppurate.

A blood specimen was taken twelve days after the development of the fever, and Francis reported that the serum agglutinated *Bacterium tularense* in all dilutions from 1:10 to 1:160, thus confirming the diagnosis of tularemia. A guinea pig inoculated with 1 c.c. of serum died in five days with the characteristic caseous inguinal nodes and spotted liver and spleen. The organism was recovered on our human serum modification of Francis' medium.

#### Case XII

Mr. A. K., age 20; meat cutter at the K. grocery. Mr. K. dressed rabbits, received from the J. O. F. market, during Thanksgiving week, 1927. On November 26 he felt that he was "coming down with the grippe" but went to work. He noticed for the first time, on that day, a small reddish papule on the inner aspect of the pad of the right thumb. After returning from work that day he had a severe chill, and he noticed for the first time painful swelling of the right axillary nodes, so much so that he was unable to raise the right arm. The next day he visited Dr. Raymond Lewis, who recognized the case as one of tularemia. The temperature at this time was 100°F., pulse 100. He was unable to work for two weeks most of which time was spent in bed. The axillary swelling reached lemon size and was surgically incised, two weeks after the onset of his illness. The patient returned to work at the end of three weeks but felt very weak during the following three months.

A specimen was sent to Francis on December 19 and he found that the serum ag-



FIG. 10. Mr. J. S., case XV. Healing ulcer of left thumb, just above nail. Six weeks after onset.



FIG. 11. Mr. J. S., case XV. Two healing ulcers on medial aspect of right index finger. Six weeks after onset.

agglutinated *Bacterium tularensis* in dilution of 1:2560. A second specimen was sent on February 15, 1928, and it was found to be positive in the same dilution.

#### Case XIII

Mrs. C. M., age 36; housewife; patient of Drs. Bowers, Arn and Huston. On November 23, Mrs. M. dressed rabbits which had been killed in the woods near her home at Waynesville, Ohio. She scratched the middle finger of the right hand while dressing the rabbits. Two days later she noticed a painful lump in the bend of the right elbow and in the right armpit. There was no visible ascending lymphangitis and she states that she did not suffer from chills or fever. The enlarged lymph nodes became very painful and on December 20 were surgically drained, followed by relief of the pain. Mrs. M. declares that she noted white spots on the liver and spleen of one rabbit which she dressed. Mrs. M.'s serum was found to agglutinate *Bacterium tularensis* in all dilutions to 1:1280 (Francis).

#### Case XIV

Mrs. I. S., age 50; housewife; patient of Dr. E. E. Bohlender. Mrs. S. dressed a Kentucky rabbit, purchased at a local market, on Tuesday, November 22, 1927. At 11:00 P. M., on November 24, she experienced a severe headache with aching pains in the back and extremities. Her temperature rose to 103°F. Dr. Bohlender saw the patient for the first time on December 9, 1927, and found a small ulcer at the tip of the right thumb, together with painful enlargements of the right epitrochlear and right axillary lymph nodes. She was prostrate for five weeks after which she was able to sit up for a few hours at a time. She has not yet (February 26, 1928) regained her strength. The ulcer on the thumb has healed; there is still an English walnut size painful axillary mass which has not supplicated. The patient lost an indeterminate amount of weight during her illness but is now regaining it.

Serum sent to Francis on December 29

was found to agglutinate *Bacterium tularensis* in all dilutions from 1:10 to 1:2560.

#### Case XV

Mr. J. S., age 38; commission merchant. On the Monday before Thanksgiving, 1927, he drove his truck to Cynthiana, Kentucky, and purchased 500 rabbits from various grocers. These had been shot by Kentucky hunters and eviscerated in the field. Mr. S. states that the rabbit hunters in Kentucky have learned to have great fear of what they term "rabbit disease" and are cautious about handling the viscera of the rabbits which they kill. They make a practice of making one longitudinal slit with a sharp knife in the mid-line of the abdomen and thorax and then, grasping the rabbit firmly by the hind legs, shake the viscera from the animal. One of the market men, from whom Mr. S. purchased most of his rabbits, threw in a dozen extra rabbits which had been lying around the market for several days, as a "gift."

Mr. S. brought his truckload of rabbits to a farm three miles from Franklin, Ohio, where he and three other men (C.D.M., A.W.E., and F.C.) skinned and partially dressed the 500 rabbits on Tuesday afternoon, November 22. On the Saturday afternoon following Thanksgiving (November 26, 1927) all four of these men became acutely ill within one hour. Mr. S. was forced to take to his bed on Saturday afternoon with "grippe-like" symptoms, a fever which rapidly mounted to 104.5°F. and severe aching pains in the extremities and back. He suffered from repeated chills and sweats. Two days after he took to his bed, he noticed two ulcers on the medial aspect of the right index finger and on ulcer on the left thumb just above the nail (see photographs). Just prior to this observation, he began to experience painful swellings in both axillae but much more marked on the right. The mass in the right axilla reached orange size in one week and became exquisitely painful, so that movements of the right upper extremity were practically impossible. Three cherry sized painful nodes appeared in the left



axilla. In both antecubital fossae enlarged epitrochlears appeared.

Just prior to Thanksgiving day, Mr. S. had distributed about 250 of his rabbits to various Dayton markets, but he discovered, to his dismay, that there was no demand for rabbits in Dayton, because of the publicity which attended the death of F. W. Consequently, on December 1, the fifth day of his illness, he got out of bed, even though he was in a very much weakened condition, and drove to Middletown and Franklin, Ohio, in an endeavor to dispose of the remaining rabbits, which he had placed in cold storage in the interim. He became so sick on this trip that he was forced to abandon the trip and his wife, who accompanied him, drove him home. He remained in bed until January 2. When seen by the writer on January 10, when he was admitted to the Miami Valley Hospital, he was extremely weak and showed evidence of considerable loss of weight, but was without febrile symptoms. The axillary masses had become fluctuant and surgical drainage was advised. Over the upper extremities and neck was found a diffuse maculo-papular eruption. On January 16, 1928, the axillary abscesses were drained and the suppurating lymphnodes were excised by Dr. H. H. Herman. Material from the lymphnodes, including fragments from the abscess walls, was placed upon our human serum modification of Francis' culture medium. Three guinea pigs were inoculated with similar material. On the third day following the inoculation of the culture media the first growth of the characteristic small spherical whitish colonies was noticed (see photograph). The next day these cultures were taken off with sterile saline solution and injected into three guinea pigs. The animals injected directly with the material from the abscesses, and the animals injected with the bacterial suspension died within five days with typical gross lesions of tularemia. From the heart's blood of two of the animals which had been injected with the culture the organism was again recovered, and when injected into two new animals caused death in four days in

one instance and in five days in the other. To further prove that the organism was *Bacterium tularense*, agglutination tests were carried out with sera from J.S., C.D.M. and Mrs. C.M. The organisms agglutinated promptly in all dilutions up to 1:1280.

Mr. S. remained in the hospital for two weeks, after which he returned to his home feeling somewhat better. The drainage continued from the left axilla for one week and from the right axilla until February 25. The patient is still weak and unable to do any physical work (March 3, 1928).

The serum of Mr. S. was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:2560. Mr. Fred Berry, Chief of Division of Laboratories, Ohio Department of Health, at Columbus, found that the serum of Mr. S. agglutinated *Bacterium tularense* in the highest titre he made, 1:1230.

#### Case XVI

Mr. C. D. M., age 22; farmer. For several years, Mr. M. has made yearly trips to Kentucky, during November, to obtain rabbits for Dayton, Ohio, markets. He accompanied Mr. S. (case No. XV) one week before Mr. S. made the trip in which he obtained the 500 rabbits which caused the disease in four people. On this trip, Mr. M. purchased 300 rabbits at Carlisle, Kentucky. These he skinned and dressed and distributed to Dayton markets without untoward event. When Mr. S. returned from Kentucky with the 500 rabbits mentioned above, on November 22, 1927, Mr. M. assisted in the preparation of the rabbits for market. While dressing the rabbits, Mr. M. pricked the skin in the web between the right thumb and index finger, on the palmar surface, with a sharp fragment of rabbit bone. On the Saturday afternoon after Thanksgiving, 1927, he developed a high fever, chills and sweats, pains in the back and extremities and noticed a painful swelling in the right axilla. The next day he noticed a reddish papule at the site of the bone prick. In two days this became a



FIG. 12. Mr. J. S., case XV. Right axillary adenopathy. Similar mass in left axilla. Six weeks after onset.

sharply punched-out ulcer,  $\frac{1}{4}$  inch in diameter. From the third to the seventh day of his illness he was delirious. He described the onset of his illness, "as though I was coming down with flu." His sister who was visiting at his home, and who had learned of this disease in Kansas last year, told the doctor who was called that her brother had "rabbit disease." The doctor questioned her diagnosis. Ten days after the ulcer developed it was surgically incised. The patient felt much worse for three days following the incision. He remained in bed until the Wednesday after Thanksgiving. He then got up, feeling very weak, but was forced to return to bed for two weeks more, after which he loafed around the house for three weeks and then returned to his work feeling quite lifeless. When examined by the writer on January 20, an orange sized fluctuating axillary mass, covered by thin skin, was found, together with a diffuse radiating lymphangitis extending beyond the anterior and posterior axillary folds. Spontaneous rupture occurred two days later. The ulcer on the hand was almost completely healed but there was still a distinct excavation at the point of inoculation (see photographs). When Mr. M. was informed as to the nature of the infection he insisted that his mother must have had the disease one year previous when she assisted him in the dressing of several hundred rabbits which he had purchased in Kentucky. Mrs. M.'s history will appear under "Cases Prior to 1927."

Francis found that Mr. M.'s serum agglutinated *Bacterium tularensis* completely at 1:640 and partially at 1:1280, in a specimen taken on January 20. At the Ohio Department of Health Laboratories, Berry found agglutination in a dilution of 1:640.

#### Case XVII

Mr. A. W. E., age 65, father-in-law of Mr. J. S. (case No. XV); farmer. Mr. E., while assisting Mr. J. S. in dressing the 500 rabbits which he had obtained in Kentucky, on the Tuesday before Thanksgiving (November 22, 1927), punctured the tip of the ring finger of the right hand, near the

nail bed, with the sharp edge of a fragment of rabbit bone. On Saturday afternoon, November 26, the finger ached, and he felt very sick and was forced to take to his bed for two days. During the two days in bed he had chills and fever and at times was delirious. He then went to see a doctor who lanced the finger several times. No pus was ever evacuated as a result of the repeated incisions. On November 26, he noticed painful sensations in the right axilla. These gradually assumed the size of a lemon. The nailbed became blackened. Mr. E. felt very sick for six weeks but when questioned by the writer on January 11 stated that he felt entirely well. When examined on January 11, the scar of the ulcer on the tip of the fourth right finger was still present together with the blackened finger nail and in the axilla was a lemon sized fluctuating mass. The skin overlying the axillary mass showed marked pyoderma (see photographs).

Francis found that Mr. E.'s serum agglutinated *Bacterium tularensis* in all dilutions up to 1:1280. Similar results were obtained in the Ohio Department of Health Laboratories by Berry.

#### Case XVIII

Mr. F. C., a negro farmer, age 40, helped Mr. S. (case No. XV) dress the 500 Kentucky rabbits on the Tuesday before Thanksgiving, 1927, and on the Saturday afternoon following Thanksgiving developed a high fever, severe backache, pains in the extremities, chills and fever, and declares that he was delirious for one week. While dressing the rabbits he stuck a sliver of rabbit bone into the fourth finger of the right hand on the medial aspect of the middle phalanx (see photograph). The resulting perforating wound refused to heal. On the Saturday after Thanksgiving, he noticed for the first time a cherry-sized lump just above the medial condyle of the right humerus. This rapidly assumed the size of an orange. At no time did he have any palpable axillary adenopathy (see photograph). He remained in bed for four weeks. When examined by the writer on February



FIG. 13. Tubes 1 and 2 show colonies of *Bacterium tularensis* resulting from direct inoculation from axillary tissue of Mr. J. S., case XV. Tubes 3 and 4 show growth obtained from axillary tissue of Mr. H. C., case XIX. Note fragment of abscess wall on media in tube 3, with typical colonies radiating from it.

2, 1928, the large epitrochlear mass was still present, together with the scar of the primary lesion. When questioned regarding the present state of his health Mr. E. replied that he was still very sick and unable to do his customary amount of work.

Serum from F. C. was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:640. The serum likewise agglutinated *Bacterium abortus* (1:80) and *Bacterium melitense* (1:80).

### Case XIX

Mr. H. C., age 20; dresser of rabbits for the E. F. market. On Monday, November 21, 1927, while dressing rabbits which had been received from Maysville, Kentucky, he accidentally cut the dorsal surface of the index finger of his right hand. The cut refused to heal. On Friday, November 25, there developed over the inner aspect of the right arm, overlying the medial aspect of the belly of the biceps brachii, three reddish and extremely painful nodules, the upper two of which assumed cherry size while the lowermost one assumed English walnut size (see photograph). The appearance of this nodular lymphangitis was not unlike sporotrichosis. At the same time he noticed painful swelling of the right axillary nodes. He was unable to get out of bed on this day, because of severe pains in the back and limbs and a very severe headache. A physician was called who incised the finger lesion. No actual pus escaped and the patient felt much worse following the incision. Two days later a nodule developed over the metacarpo-phalangeal articulation of the right index finger, one-half inch above the primary lesion. This too was incised by his physician. The primary lesion became larger; the center became necrotic and sloughed out, leaving an irregular deep ulcer about 3x1 cm. (see photograph). The patient's fever mounted to 105°F.; he suffered from three to five severe chills each day for five days, each chill followed by a drenching sweat. For four days he was delirious and his life was despaired of. He was severely ill for two weeks during which time he remained constantly in bed. At the end of this time he felt somewhat better and

tried to get up but was unable to walk because of weakness. During the next month he spent a part of each day walking about the house but was forced to lie down from time to time because of weakness. He was still too weak to work when last examined (March 1, 1928).

On January 17, 1928, Mr. C. was admitted to the Miami Valley hospital for excision of the axillary mass and for drainage of the nodules overlying the mesial aspect of the biceps. The axillary mass was removed intact by Dr. E. R. Arn. Three guinea pigs were inoculated at once with the material from the axillary nodes and several tubes containing our human serum modification of Francis' medium were inoculated directly with the purulent fluid and with granulomatous tissue from the abscess walls. Three days later the first growth was noticed. In one of the tubes in which a pea-sized fragment of tissue from the abscess wall had been placed small spherical whitish colonies were seen to radiate from the tissue. (See photograph.) Growth was obtained on five of the six tubes inoculated. To prove that the organism was *Bacterium tularensis* the same procedure was carried out as in the J. S. case (case No. XV) and every requirement for the identity of the organism was satisfied.

Microscopic examination of the tissue from the axilla showed large areas of caseation necrosis, with well defined fibroblastic and epithelioid granulation tissue at the periphery. There were large Langhans' foreign-body giant cells in the epithelioid granulation tissue. There was no angioblastic proliferation in the granulation tissue.

The serum of Mr. H. C., collected on January 14, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions up to 1:1280. At the Ohio State Health Laboratories, Berry obtained the same results.

### Case XX

Mr. C. J. P., age 25, dressed rabbits at the E. F. market. He cut the skin of his right thumb, over the middle of the proximal phalanx, with a rabbit bone, on November 17, 1927. The wound in the thumb re-

fused to heal. Four days after the initial injury, an English walnut size mass appeared in the right axilla. He felt quite ill, but did not quit work even though he was unable to use the right hand and arm. He had a severe headache and backache but

#### Case XVI

Mr. A. L. G., age 34, dressed rabbits at an Atlantic and Pacific Tea Company's store in Dayton, on November 18, 1927. These rabbits had been received from the J. O. F. market, which means that they were Mays-



FIG. 14. Mr. C. D. M., case XVI. Healing ulcer in web between right thumb and index finger, eight weeks after onset.

does not think that he had a high fever. He feels perfectly well now. There is still present in the right axilla a firm English walnut sized mass showing no tendency to suppurate. Serum was not obtained until February 17, just three months after the inoculation of his thumb. It was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:320.

ville, Kentucky, rabbits. While dressing the rabbits, he stuck the sharp edge of a meat hook under the finger nail of the middle finger of the right hand. His finger became somewhat swollen and began to discharge serous material within twenty-four hours. Two days after the injury to his finger, he experienced a very severe chill, followed by a drenching sweat. His fever became

very high; he had repeated chills and sweats for ten days, accompanied by severe body aches and headache. On the day following the first severe chill he noticed a painful mass in the right axilla, to which flax seed poultices were applied for three days. At first there were two hickory nut sized masses, which later became confluent and formed a lemon-sized mass (see photograph). Because of economic difficulties he felt forced to work through the period of his illness but returned to his home every night completely exhausted.

On February 20, 1928, Mr. G. was admitted to the Miami Valley hospital, where the axillary mass was removed intact by Dr. E. R. Arn. All attempts to recover the organism by animal passage and by the inoculation of culture media, were unsuccessful. Serum collected on February 7 was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:1280.

Microscopic examination of axillary tissue sections showed large areas of caseation necrosis, surrounded by a broad zone of avascular fibroblastic and epithelioid granulation tissue, containing occasional Langhans' giant cells. There was endothelial proliferation, with partial obliteration of the venules and arterioles.

#### Case XXII

Mr. E. A. M., a patient of Drs. W. and C. J. Ryan and Dr. Joseph O. Porter, age 67, a retired farmer, killed several rabbits in the woods three miles northeast of Eaton, Ohio, on November 16, 1927. He dressed the rabbits in the field. The patient remembers distinctly that the livers were dotted with small whitish spots. On November 18 he noticed a small papule on the dorsal surface of the web between the thumb and index finger of the left hand. Several hours later he noticed another papule on the same hand on the lateral surface of the ring finger overlying the distal interphalangeal articulation. These gave practically no pain. On the afternoon of November 18, the patient began to feel drowsy and depressed. In the evening he had a chill. The next morning he felt rather weak but thought

he might wear it off by hunting. He went out for a short time but felt forced to return and go to bed. The following morning the arm was markedly swollen and very painful. He had a high fever, and a rapid pulse, with repeated chills and sweats. His wife states that he was "out of his head" part of the time. In the evening a painful swelling developed in the left axilla and there were distinct reddish-blue streaks in the skin of the inner aspect of the arm. Several painful nodules developed along these streaks. The mass over the arm finally reached the size of a hen's egg.

When seen upon December 6, the patient was very anemic, toxic, and had lost considerable weight. He was highly nervous, irritable, and greatly depressed. He was convinced that he could not live. The primary lesion on his left hand was covered by a crust. When this was removed there remained a deep, sharply punched-out ulcer. On January 17, the patient was again seen by his physician who found him in good spirits. He had regained ten pounds but felt weak at times. The lesion on the left hand was practically healed but the axillary mass was not greatly reduced in size.

The serum of Mr. M., taken on December 1, 1927, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:180.

#### Case XXIII

Mrs. F. A. S., age 42; housewife; patient of Dr. N. C. Hochwalt. Mrs. S. was presented with a rabbit which had been brought from Kentucky. She prepared the rabbit for cooking on the evening of November 28, 1927, and cut her thumb with a sharp fragment of rabbit bone. During the afternoon of November 30 she complained of chills, fever, and generalized aching sensations. On December 2, she complained of soreness of the palmar surface of the distal phalanx of the right thumb; the fever and aching continued. The patient was first seen by Dr. Hochwalt on the morning of December 2. Examination revealed a slight swelling of the distal phalanx of the right thumb, together with enlargement of the epitrochlear glands. There was no axillary swell-

ing. The temperature at this time was 103° F., pulse 120. The patient remained in bed for four weeks during which time the temperature varied from 99° to 103° F. The area on the thumb became ulcerated with central necrosis while the epitrochlear glands assumed the size of a robin's egg.

On February 8, 1928, the ulcerated area on the thumb was smaller but not yet healed and was still painful. The epitrochlear mass had not diminished in size and was still tender. *There was no axillary involvement at any time.*

Serum of Mrs. S., taken on February 8, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:1640.

### B. Cases Prior to 1927

Many Dayton physicians indicated to the writer that they had seen patients in previous years who had unquestionably been victims of this disease. The writer visited these individuals and in nearly every case elicited a very characteristic history. A circular letter was sent to all of the physicians of the city asking for information regarding old possible cases of tularemia. As result of this letter six old cases were discovered, all among market men. The writer then visited each of the larger markets of the city and talked with the proprietors regarding cases of "rabbit fever." As a result of these investigations, 25 cases occurring prior to 1927 were unearthed. It was definitely established that tularemia has been present in this city for twenty years.

#### Case XXII

Mr. M. T., age 55; wholesale produce dealer. During November of 1908, while dressing rabbits; he cut his right hand with a rabbit bone, three days after which he became acutely ill and suffered from chills and

sweats, high fever, prostration and enlarged right axillary lymphnodes. The rabbits were purchased from B. L. Co., of St. Louis, Missouri, and the rabbits had been killed in Missouri and Kansas.

Serum collected on February 13, 1928, 19 years and 3 months following the onset of the disease, was found to agglutinate *Bacterium tularense* in all dilutions to 1:160 (Francis).

This is the earliest case of tularemia of which there is any record east of the Mississippi river.

#### Case XXV

Mr. J. H. A., age 68. Just before Thanksgiving time, 1912, he scratched his hands with rabbit bones while dressing rabbits in the F. market of Dayton. On the Sunday before Thanksgiving, 1912, he was taken suddenly ill with a high fever, chills and sweats, and great prostration. He remained in bed for one month, during which time he suffered from a severe watery diarrhea. Huge axillary masses, of orange size, developed in both axillae, together with a cherry sized mass in the right epitrochlear area. Three weeks after the onset of his illness the axillary masses were surgically drained and the drainage continued for many weeks. He was unable to return to his work until the following April. He did not feel well for over a year.

Serum of Mr. A., collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

#### Case XXVI

Mr. J. C., age 50, dressed rabbits at the F. market during Thanksgiving week, 1913. Three days later he experienced a severe chill, followed by sweats and a rapidly mounting fever. His doctor felt that he was acquiring "grippe." In the right axilla there developed multiple cherry sized painful swellings. No ulcer developed at any time on the right hand. Mr. C. was incapacitated for work for three weeks, and after he returned to his work felt exhausted for many weeks.

Serum of Mr. C., collected on March 14,



TABLE II  
Cases Prior to 1927

Case No.	Initials	Sex	Age	Occupation	Source of Infection	Primary Lesion	Incubation Period	Onset Date	Adenopathy	Suppuration	Agglutination (by Francis)	Convalescence	Type
21	M.T.M.	M	55	Produce dealer	Missouri and Kansas rabbits	Right hand	3 days	Nov., 1908	Right axillary	None	1:160	Many weeks	UG
22	J.H.M.	M	58	Market man	Kentucky and Ohio rabbits	Both hands	3-4 days	Nov., 1912	Right and left axillary, right epitrochlear	Incision	1:80	Five months	UG
23	J.C.M.	M	50	Market man	Kentucky and Ohio rabbits	No ulcer	Three days	Nov., 1913	Right axillary	None	1:320	Short	0
24	B.K.M.	M	38	Butcher	Kentucky rabbits	Left thumb	4-5 days	Nov., 1914	Right and left axillary, left epitrochlear	Incision		46 days plus	UG
25	R.T.M.	M	51	Market man	Kentucky rabbits	Right thumb, left hand	Two days	Nov., 1916	Right and left axillary	Incision	1:320	Several months	UG
26	B.F.M.	M	54	Market man	Missouri rabbits	Left middle finger	Four days	Nov., 1916	Questionable		1:320	Six months	?
27	O.F.M.	M	49	Market man	Kentucky rabbits	Palm, left hand	3-4 days	Nov., 1916	Left axilla	Spontaneous	1:160	5 weeks plus	UG
28	O.F.F.	M	43	Proprietor of market	Missouri and Kansas rabbits	No ulcer	Three days	Nov. 11, 1916	Right and left axillary	Incision	1:80	Several weeks	0
29	E.M.M.	M	41	Market man	Missouri and Kansas rabbits	Left index finger	Three days	Nov. 11, 1916	Left axillary	Incision	1:320	Eight months	UG
30	C.F.M.	M	40	Market man	Missouri and Kansas rabbits	Right thumb	Six days	Nov. 14, 1916	Right axillary	Incision	1:20	Five months	UG
31	H.S.M.	M	42	Market man	Kentucky rabbits	Right index finger	Four days	Nov., 1919	Right axillary and epitrochlear	None	1:80	Four months	UG
32	W.E.M.	M	38	Merchant	Local rabbits	Right hand	1-2 days	Nov., 1920	Right axillary	None	1:40	One month	UG
33	W.H.M.	M	50	Market man	Kentucky rabbits	Left middle finger	Three days	Nov., 1922	Right and left axillary	Incision spontaneous	1:160	Three months plus	UG
34	P.R.M.	M	46	Butcher	Kentucky rabbits	Right index finger	Two days	Nov., 1922	Right axillary	None	1:160	One year	UG
35	I.A.M.	M	45	Butcher	Kentucky rabbits	None	Five days	Nov., 1922	Left axillary	Excised	1:40	Six months	0
36	W.F.M.	M	38	Market man	Kentucky rabbits	Left ring finger	Two days	Nov. 13, 1922	Left axillary and epitrochlear	Incised	1:80	Four months	UG
37	J.R.M.	M	47	Market man	Missouri rabbits	Right middle finger	Four days	Nov. 19, 1923	Right axillary	Incised	1:320	10 weeks plus	UG
38	M.H.F.	F	55	Rabbit dresser	Kentucky rabbits	None	Unknown	Nov., 1923	Right axillary and epitrochlear	None	1:80	Several months	UG
39	W.R.F.	F	48	Rabbit dresser	Kentucky rabbits	None	Unknown	Nov., 1923	Right axillary and epitrochlear	Incision	1:80	Four months	0
40	D.J.M.	M	30	Market man	Kentucky rabbits	Left fifth finger	Seven days	Nov., 1924	Left axilla	Incision	1:160	Several months	UG
41	DeB.F.	F	38	Rabbit dresser	Kentucky rabbits	Left thumb	Four days	Nov., 1924	Left epitrochlear and axillary; nodular lymphangitis	Incision and spontaneous	1:80	Five months	UG
42	J.H.F.	M	54	Market man	Kentucky rabbits	Right thumb	Four days	Nov., 1925	Right axillary	Incision	1:160	Months plus	UG
43	J.S.M.	M	36	Butcher	Kentucky rabbits	Between right middle and ring finger	One day	Nov. 26, 1925	Right axillary and epitrochlear	Incision	1:160; partial 1:320	Several weeks	UG
44	C.R.M.	M	39	Butcher	Kentucky rabbits	Left little finger	Five days	Nov. 21, 1926	Left and right axillary; left and right epitrochlear	Incision	1:80	Six months	UG
45	M.W.F.	F	56	Housewife	Kentucky rabbits	Right fourth finger	Two days	Nov., 1926	Right axillary	None	1:320	Several months	UG
							0 = Glandular type		UG = Ulceroglandular type				

1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

#### Case XXVIII

Mr. B. K., age 38, dressed rabbits at the A. market at Thanksgiving time, 1917. He scratched the left thumb with either a knife or a sharp rabbit bone. Four days later he developed a fever of 104 F. with chills, sweats, severe backache and headache. He remained in bed for 16 days. Lemon sized painful axillary swellings developed on both sides. In the left epitrochlear region a lemon size painful swelling developed. All 3 of the masses were surgically drained by Dr. A. H. Dunham. Mr. K. was unable to return to his work for 40 days after the onset.

#### Case XXVIII

Mr. R. T., age 51, dressed Kentucky rabbits at the F. market during the four days before Thanksgiving of 1916. He stuck sharp fragments of rabbit bones into the tip of the right thumb, into the thenar eminence of the left hand and into the palmar surface of the web between the thumb and index finger of the left hand. Two days later he had a severe chill and severe aching sensations in the back and extremities. He states, "I thought the flu was coming over me." He took to his bed, where he remained for two weeks. Two days after taking to his bed, he noticed painful swellings in both axillae. The mass in the right axilla assumed the size of an orange, while that in the left axilla became of hen's egg size. Two weeks after the onset of his illness the mass in the right axilla was drained surgically. The patient lost 20 pounds during the first two weeks of his illness. In view of the fact that he weighed 108 pounds prior to his illness, this represents a considerable loss. He did not regain his strength for over one year.

Serum of Mr. T., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

#### Case XXIX

Mr. B. F., age 64, dressed rabbits which had been received from St. Louis at the F.

market during Thanksgiving week, 1916. He stuck the sharp point of a fragment of rabbit bone into the palmar surface of the skin of the left middle finger overlying the proximal phalanx. Four days later the hand became greatly swollen, reddish-blue streaks ascended the arm and he felt very weak. His powers of recall are poor and he does not remember whether there were any epitrochlear or axillary swellings. He was out of work for six months. The finger was incised surgically many times with a resulting permanent ankylosis of both interphalangeal articulations.

Serum of Mr. F., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

#### Case XXX

Mr. O. F., age 49, dressed rabbits at the F. market, Dayton, during the month of November, 1918. On the day after Thanksgiving, 1918, he was taken suddenly ill with a disease which was diagnosed "grippe." Just before Thanksgiving day he had stuck the sharp edge of a turkey bone into the palm of the left hand. At the same time that he was taken ill, a mass appeared in the left axilla and assumed the size of a hen's egg. This mass drained spontaneously after about one month and caused him great pain until the following February. The axillary drainage continued for five weeks. For economic reasons he did not go to bed during his entire illness, although he admits that he was much too sick to work.

Serum of Mr. F., collected on February, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

#### Case XXXI

Mr. O. F. F., age 43, proprietor of F. market, Dayton, dressed rabbits which had been received from B. L. company, St. Louis, on November 8, 1918. The rabbits had been killed in Missouri and Kansas. On Armistice day (November 11, 1918) he was taken suddenly ill and was forced to take to his bed. While dressing rabbits he had scratched both hands in many places but does not remember any papules or ulcers on either

TABLE II  
Cases Prior to 1927

Case No.	Initials	Sex	Age	Occupation	Source of Infection	Primary Lesion	Incubation Period	Onset Date	Adenopathy	Suppuration	Agglutination (by Francis)	Convalescence	Type
21	M.T.M.	M	55	Produce dealer	Missouri and Kansas rabbits	Right hand	3 days	Nov., 1908	Right axillary	None	1:160	Many weeks	UG
22	J.H.A.	M	38	Market man	Kentucky and Ohio rabbits	Both hands	3-4 days	Nov., 1912	Right and left axillary, right epitrochlear	Incision	1:80	Five months	UG
23	J.C.M.	M	50	Market man	Kentucky and Ohio rabbits	No ulcer	Three days	Nov., 1913	Right axillary	None	1:320	Short	O
24	R.K.M.	M	38	Butcher	Kentucky rabbits	Left thumb	4-5 days	Nov., 1914	Right and left axillary, left epitrochlear	Incision		45 days plus	UG
25	R.T.M.	M	51	Market man	Kentucky rabbits	Right thumb, left hand	Two days	Nov., 1916	Right and left axillary	Incision	1:320	Several months	UG
26	R.F.M.	M	54	Market man	Missouri rabbits	Left middle finger	Four days	Nov., 1916	Questionable		1:320	Six months	1
27	O.F.M.	M	49	Market man	Kentucky rabbits	Palm, left hand	3-4 days	Nov., 1916	Left axilla	Spontaneous	1:160	5 weeks plus	UG
28	O.E.M.	M	43	Proprietor of market	Missouri and Kansas rabbits	No ulcer	Three days	Nov. 11, 1916	Right and left axillary	Incision	1:80	Several weeks	O
29	E.M.M.	M	41	Market man	Missouri and Kansas rabbits	Left index finger	Three days	Nov. 11, 1916	Left axillary	Incision	1:320	Eight months	UG
30	C.F.M.	M	40	Market man	Missouri and Kansas rabbits	Right thumb	Six days	Nov. 14, 1916	Right axillary	Incision	1:20	Five months	UG
31	R.S.M.	M	42	Market man	Kentucky rabbits	Right index finger	Four days	Nov., 1919	Right axillary and epitrochlear	None	1:80	Four months	UG
32	W.E.M.	M	38	Merchant	Local rabbits	Right hand	1-2 days	Nov., 1920	Right axillary	None	1:40	One month	UG
33	W.H.M.	M	50	Market man	Kentucky rabbits	Left middle finger	Three days	Nov., 1922	Right and left axillary	Incision spontaneous	1:160	Three months plus	UG
34	P.N.M.	M	46	Butcher	Kentucky rabbits	Right index finger	Two days	Nov., 1922	Right axillary	None	1:160	One year	UG
35	I.A.M.	M	45	Butcher	Kentucky rabbits	None	Five days	Nov., 1922	Left axillary	Excised	1:40	Six months	O
36	W.F.M.	M	38	Market man	Kentucky rabbits	Left ring finger	Two days	Nov. 13, 1922	Left axillary and epitrochlear	Incised	1:80	Four months	UG
37	J.R.M.	M	47	Market man	Missouri rabbits	Right middle finger	Four days	Nov. 19, 1923	Right axillary	Incised	1:320	10 weeks plus	UG
38	M.N.F.	F	55	Rabbit dresser	Kentucky rabbits	None	Unknown	Nov., 1923	Right axillary and epitrochlear	None	1:80	Several months	UG
39	W.R.F.	F	48	Rabbit dresser	Kentucky rabbits	None	Unknown	Nov., 1923	Right axillary and epitrochlear	Incision	1:80	Four months	O
40	J.M.	M	30	Market man	Kentucky rabbits	Left fifth finger	Seven days	Nov., 1924	Left axilla	Incision	1:160	Several months	UG
41	Ed.R.F.	F	38	Rabbit dresser	Kentucky rabbits	Left thumb	Four days	Nov., 1924	Left epitrochlear and axillary; nodular lymphangitis	Incision and spontaneous	1:80	Five months	UG
42	J.P.M.	M	54	Market man	Kentucky rabbits	Right thumb	Four days	Nov., 1925	Right axillary	Incision	1:160	5 months plus	UG
43	J.G.S.	M	36	Butcher	Kentucky rabbits	Between right middle and ring finger	One day	Nov. 26, 1926	Right axillary and epitrochlear	Incision	1:160; partial 1:320	Several weeks	UG
44	C.B.M.	M	39	Butcher	Kentucky rabbits	Left little finger	Five days	Nov. 21, 1926	Left and right axillary; left and right epitrochlear	Incision	1:80	Six months	UG
45	M.M.F.	F	56	Housewife	Kentucky rabbits	Right fourth finger	Two days	Nov., 1926	Right axillary	None	1:320	Several months	UG

O = Olandular type

UG = Uteroglandular type

1928, was found by Francis to agglutinate *Bacterium tulareense* in all dilutions to 1:320.

#### Case XXVII

Mr. B. K., age 38, dressed rabbits at the A. market at Thanksgiving time, 1914. He scratched the left thumb with either a knife or a sharp rabbit bone. Four days later he developed a fever of 104°F. with chills, sweats, severe backache and headache. He remained in bed for 16 days. Lemon sized painful axillary swellings developed on both sides. In the left epitrochlear region a lemon size painful swelling developed. All 3 of the masses were surgically drained by Dr. A. H. Dunham. Mr. K. was unable to return to his work for 46 days after the onset.

#### Case XXVIII

Mr. R. T., age 51, dressed Kentucky rabbits at the F. market during the four days before Thanksgiving of 1916. He stuck sharp fragments of rabbit bones into the tip of the right thumb, into the thenar eminence of the left hand and into the palmar surface of the web between the thumb and index finger of the left hand. Two days later he had a severe chill and severe aching sensations in the back and extremities. He states, "I thought the flu was coming over me." He took to his bed, where he remained for two weeks. Two days after taking to his bed, he noticed painful swellings in both axillae. The mass in the right axilla assumed the size of an orange, while that in the left axilla became of hen's egg size. Two weeks after the onset of his illness the mass in the right axilla was drained surgically. The patient lost 20 pounds during the first two weeks of his illness. In view of the fact that he weighed 108 pounds prior to his illness, this represents a considerable loss. He did not regain his strength for over one year.

Serum of Mr. T., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tulareense* in all dilutions to 1:320.

#### Case XXIX

Mr. B. F., age 64, dressed rabbits which had been received from St. Louis at the F.

market during Thanksgiving week, 1916. He stuck the sharp point of a fragment of rabbit bone into the palmar surface of the skin of the left middle finger overlying the proximal phalanx. Four days later the hand became greatly swollen, reddish-blue streaks ascended the arm and he felt very weak. His powers of recall are poor and he does not remember whether there were any epitrochlear or axillary swellings. He was out of work for six months. The finger was incised surgically many times with a resulting permanent ankylosis of both interphalangeal articulations.

Serum of Mr. F. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tulareense* in all dilutions to 1:320.

#### Case XXX

Mr. O. F., age 49, dressed rabbits at the F. market, Dayton, during the month of November, 1918. On the day after Thanksgiving, 1918, he was taken suddenly ill with a disease which was diagnosed "grippe." Just before Thanksgiving day he had stuck the sharp edge of a turkey bone into the palm of the left hand. At the same time that he was taken ill, a mass appeared in the left axilla and assumed the size of a hen's egg. This mass drained spontaneously after about one month and caused him great pain until the following February. The axillary drainage continued for five weeks. For economic reasons he did not go to bed during his entire illness, although he admits that he was much too sick to work.

Serum of Mr. F., collected on February, 1928, was found by Francis to agglutinate *Bacterium tulareense* in all dilutions to 1:160.

#### Case XXXI

Mr. O. F. F., age 43, proprietor of F. market, Dayton, dressed rabbits which had been received from B. L. company, St. Louis, on November 8, 1918. The rabbits had been killed in Missouri and Kansas. On Armistice day (November 11, 1918) he was taken suddenly ill and was forced to take to his bed. While dressing rabbits he had scratched both hands in many places but does not remember any papules or ulcers on either

## Case XXXII

hand. On the day on which he was taken sick he noticed lemon sized, excruciatingly painful masses in both axillae. He remained in bed for one week, during which time he suffered from chills and sweats and a moderately high fever. The axillary masses were drained surgically within a few

Mr. E. M., age 41, dressed rabbits with O. F. F. (case XXXI). On Armistice Day, 1918, a reddish papule developed on the medial aspect of the distal phalanx of the left index finger. He does not remember cutting or scratching his hands while dress-

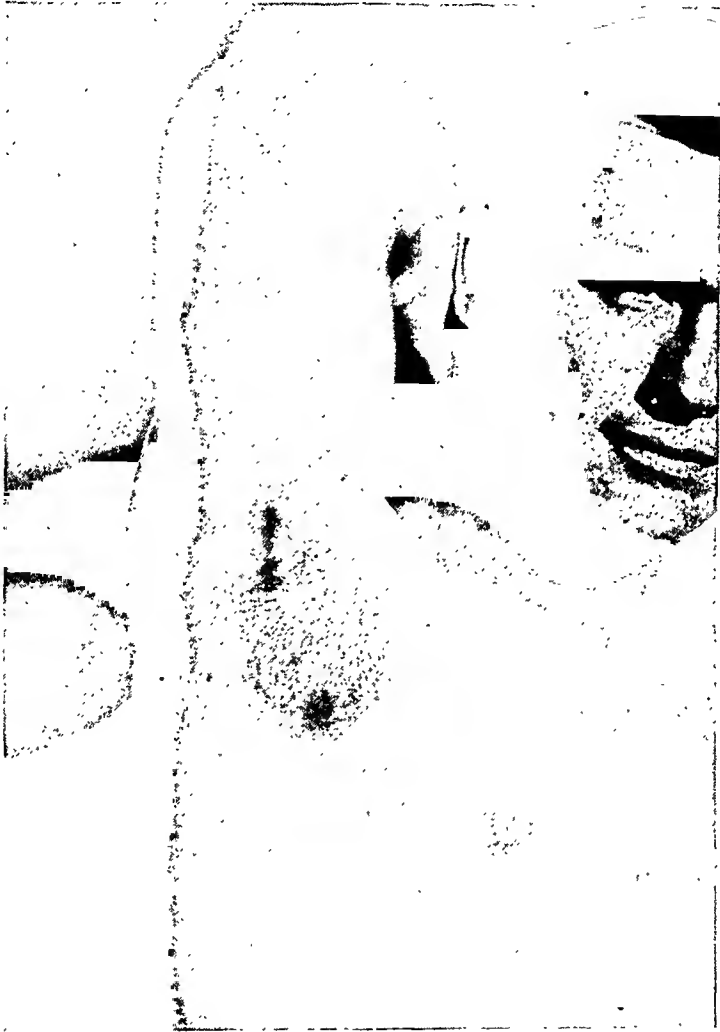


FIG. 15. Mr. C. D. M., case XVI. Axillary adenopathy. Spontaneous rupture occurred two days after photograph was taken, eight weeks after onset.

days of the onset of his illness. The drainage continued for three weeks. He returned to his work at the end of one week, still feeling quite ill.

Serum of Mr. F. collected on February 25, 1928, was found by Dr. Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

ing the rabbits. While walking on the street on Armistice day, he fainted. He was confined to his bed for 17 days with a fever which remained around 104°F. The center of the papule on the finger became necrotic and sloughed out after one week. He did not notice any mass in the left axilla until 18 days after the onset of his illness. He

to his bed. He was unable to return to his work for five months. The axillary glands were not incised nor did they rupture through the skin.

Serum of Mr. S. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

Case XXXIV

Mr. W. E., age 38, patient of Dr. A. B. Brower, injured the back of the right hand while dressing rabbits during Thanksgiving week, 1920. From 24 to 48 hours after the initial injury painful right axillary swelling occurred, accompanied by fever and chills. He did not go to bed, but was unable to use the hand and arm for one month. He did not do any work during that time.

Serum of Mr. E., collected on February 24, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:40.

Case XXXVI

Mr. W. H., age 60, dressed rabbits at the F. market during Thanksgiving week of 1922. He cut the tip of the middle finger of the left hand with a rabbit bone. Three days after this injury a painful mass appeared in the left axilla which gradually assumed the size of a grape fruit. A similar mass, which reached orange size, appeared in the right arm pit. A small deep ulcer developed at the site of the injury to his finger. Simultaneously with the development of the axillary masses he experienced repeated chills and sweats, an exceedingly high fever, and was delirious for two weeks. He was strictly confined to bed for 12 weeks. The mass in the left axilla was drained surgically two weeks after the onset of his illness. The mass in the right axilla drained spontaneously about one month after the onset of his illness. Mr. H. was unable to return to his work for three months. He did not regain his former strength, and was unable to completely elevate either arm for over one year.

Serum of Mr. H. collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:160.

excellent health.

Serum of Mr. M., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:320.

Case XXXIII

Mr. C. F., age 40, likewise assisted Mr. O. F. F. (case XXXI) in the dressing of the St. Louis rabbits. He cut the right thumb on a rabbit bone on November 8, 1928. The cut refused to heal. Six days following the injury he was forced to take to his bed because of high fever and chills. He was delirious for five days. He has no recollection as to what occurred during that period. After he had been in bed for one week the right axillary glands became large and painful. These were incised and continued to drain for three months. He did not return to his work for 5 weeks. He tired very easily and was unable to do the amount of work to which he was accustomed for five months, after which time he slowly improved.

Serum of Mr. F. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:20.

Case XXXVII

Mr. H. S., age 42, dressed rabbits which had been received from Louisville, Kentucky, at the F. market just prior to Thanksgiving, 1919. He scratched the right index finger with a sharp rabbit bone. Four days later he developed what he considered to be "cripple." A doctor was called who pronounced it "blood poisoning." He suffered from chills, high fever, severe headache and body aches for two weeks. He states that he was very weak for four months. The right axillary and epitrochlear glands were greatly swollen when he took

was unable to do any work for one month. He was then able to work from three to four hours a day until the next July when he did a full day's work for the first time. The primary lesion and the axillary mass were surgically incised, the latter on December 31, 1918. The drainage continued until July, 1919. He felt very weak until the following September. He is now in excellent health.

Serum of Mr. M., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

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#### Case XXXII

Mr. H. S., age 42, dressed rabbits which had been received from Louisville, Kentucky, at the F. market just prior to Thanksgiving, 1919. He scratched the right index finger with a sharp rabbit bone. Four days later he developed what he considered to be "grippe." A doctor was called who pronounced it "blood poisoning." He suffered from chills, high fever, severe headache and body aches for two weeks. He states that he was very weak for four months. The right axillary and epitrochlear glands were greatly swollen when he took

to his bed. He was unable to return to his work for five months. The axillary glands were not incised nor did they rupture through the skin.

Serum of Mr. S. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

#### Case XXXV

Mr. W. E., age 38, patient of Dr. A. B. Brower, injured the back of the right hand while dressing rabbits during Thanksgiving week, 1920. From 24 to 48 hours after the initial injury painful right axillary swelling occurred, accompanied by fever and chills. He did not go to bed, but was unable to use the hand and arm for one month. He did not do any work during that time.

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Serum of Mr. H. collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

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#### Case XXXII

Mr. E. M., age 41, dressed rabbits with O. F. F. (case XXXI). On Armistice Day, 1918, a reddish papule developed on the medial aspect of the distal phalanx of the left index finger. He does not remember cutting or scratching his hands while dress-



FIG. 15. Mr. C. D. M., case XVI. Axillary adenopathy. Spontaneous rupture occurred two days after photograph was taken, eight weeks after onset.

days of the onset of his illness. The drainage continued for three weeks. He returned to his work at the end of one week, still feeling quite ill.

Serum of Mr. F. collected on February 25, 1928, was found by Dr. Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

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was unable to do any work for one month. He was then able to work from three to four hours a day until the next July when he did a full day's work for the first time. The primary lesion and the axillary mass were surgically incised, the latter on December 31, 1918. The drainage continued until July, 1919. He felt very weak until the following September. He is now in excellent health.

Serum of Mr. M., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:320.

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Mr. C. F., age 40, likewise assisted Mr. O. F. F. (case XXXI) in the dressing of the St. Louis rabbits. He cut the right thumb on a rabbit bone on November 8, 1918. The cut refused to heal. Six days following the injury he was forced to take to his bed because of high fever and chills. He was delirious for five days. He has no recollection as to what occurred during that period. After he had been in bed for one week the right axillary glands became large and painful. These were incised and continued to drain for three months. He did not return to his work for 5 weeks. He tired very easily and was unable to do the amount of work to which he was accustomed for five months, after which time he slowly improved.

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to his bed. He was unable to return to his work for five months. The axillary glands were not incised nor did they rupture through the skin.

Serum of Mr. S. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

#### Case XXXV

Mr. W. E., age 38, patient of Dr. A. B. Brower, injured the back of the right hand while dressing rabbits during Thanksgiving week, 1920. From 24 to 48 hours after the initial injury painful right axillary swelling occurred, accompanied by fever and chills. He did not go to bed, but was unable to use the hand and arm for one month. He did not do any work during that time.

Serum of Mr. E., collected on February 24, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:40.

#### Case XXXVI

Mr. W. H., age 60, dressed rabbits at the F. market during Thanksgiving week of 1922. He cut the tip of the middle finger of the left hand with a rabbit bone. Three days after this injury a painful mass appeared in the left axilla which gradually assumed the size of a grape fruit. A similar mass, which reached orange size, appeared in the right armpit. A small deep ulcer developed at the site of the injury to his finger. Simultaneously with the development of the axillary masses he experienced repeated chills and sweats, an exceedingly high fever, and was delirious for two weeks. He was strictly confined to bed for 12 weeks. The mass in the left axilla was drained surgically two weeks after the onset of his illness. The mass in the right axilla drained spontaneously about one month after the onset of his illness. Mr. H. was unable to return to his work for three months. He did not regain his former strength, and was unable to completely elevate either arm for over one year.

Serum of Mr. H. collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:160.

*Case XXXVII*

Mr. P. H., a market man, age 46, scratched the right index finger, medial aspect of the distal phalanx, while dressing rabbits on the Tuesday before Thanksgiving, 1922. These rabbits had been brought

size in the right axilla. He could not remain in bed because of shooting, pounding pains in his head. The finger lesion was Dakinized repeatedly. It was treated by his doctor daily for 49 days. The axillary mass was not incised nor did it break



FIG. 16. Mr. A. W. E., case XVII. Healing ulcer of tip of right ring finger, with necrotic nail. Six weeks after onset.

to Dayton from Maysville, Kentucky. On Thanksgiving forenoon, he felt that he was "coming down with grippe" and with "rheumatic pains" in the right shoulder. The next morning he came to work at 9 o'clock. Just after arriving at his market, "everything went black and I had a real chill." He went home and went to bed. In the afternoon he noticed a mass of hen's egg

through the skin. He dragged himself around for one year feeling as though he had lost his strength. He is now a huge, muscular individual.

Serum of Mr. H., collected on February 17, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:160.

## Case XXXVIII

Mr. I. A., age 45, assisted Mr. P. H. (case XXXVII) in dressing the Maysville, Kentucky, rabbits on the Tuesday before Thanksgiving, 1922. Mr. A. is convinced that there was no scratch or cut on his hand or fingers as a result of any injury acquired while dressing rabbits. On the Sunday after Thanksgiving his left arm became very sore, with excruciating pain radiating from the left axilla. On the next day he developed a high fever, but felt forced to go to work. On Tuesday, he had to quit work and take to his bed. He noticed for the first time on this day a left axillary swelling, which assumed lemon size. On the following Sunday he developed chills and sweats and his fever increased and he was delirious for many days. His condition was diagnosed pneumonia. He remained in bed until the day after Christmas of 1922. He went to work on the first of March, 1923, but after two weeks was forced to quit because of the painful axillary mass. This mass was excised on March 15. He was unable to return to his work until the first of May. During his illness he lost 12 pounds.

Serum of Mr. A. taken on February 15, 1928, was found by Francis to agglutinate *Bacterium tularensis* in dilutions to 1:40.

## Case XXXIX

Mr. W. F., age 38, acquired the disease while dressing rabbits at the F. market, on November 11, 1922. On November 13, 1922, the left axillary glands became enlarged to lemon size. Several of the left epitrochlear glands reached cherry size. A small papule appeared at the same time on the left ring finger, which soon became ulcerated, leaving a dime size deep depression. The first symptom was a severe chill followed by a drenching sweat and high fever. He states that he felt that he was "coming down with grippe." The primary lesion was not incised but the axillary glands were surgically drained by Dr. R. R. Shank. Mr. F. was unable to return to his work because of extreme weakness until March 1, 1923. When examined on February 27, 1928, a hazelnut sized firm epitrochlear gland still remained.

Serum of Mr. F., collected on February 28, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

## Case XL

Mr. J. H., age 47, dressed rabbits which had been shipped to Dayton, from St. Louis, Missouri, on November 15, 1923. He stuck the sharp edge of a broken rabbit bone into the palmar surface of the middle finger of the right hand overlying the metacarpophalangeal articulation. He immediately put turpentine on the finger lesion. It is an old belief among market men that turpentine is the best remedy to use in order to avoid "rabbit fever." The finger lesion refused to heal. Four days later, bluish-red streaks appeared over the flexor surface of the forearm, and he experienced a severe chill, followed by a fever which went to 105°; he was delirious for four days and suffered from a severe headache and back pains. Two days after the onset of his illness his doctor noticed a mass in the right axilla. He remained in bed for seven days, after which he got up, against his doctor's orders, in order that he might go to his home in Columbus. Immediately upon arriving home he went to bed for two weeks more. He tried to "bring the mass in the armpit to a head" with poultices, but the mass seemed to become larger and reached the size of a hen's egg. It was surgically drained three weeks after the onset of his illness. It continued to drain for seven weeks. He was out of work for ten weeks and when he returned to work felt very weak for three months. He lost 40 pounds during his ten weeks' illness.

Serum of Mr. H., collected on February 20, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:320.

## Case XLI

Mrs. M. H., age 55, the mother of H. H. (case V), dressed rabbits at the C. market during the week before Thanksgiving, 1923. She does not remember any primary lesion on her hand and is quite certain that she acquired no scratches or cuts while dressing the rabbits. On Thanksgiving, 1923, she

suffered from chills and fever, but did not feel that she could go to bed because of pressing duties. She noticed painful swellings in the right axilla and epitrochlear glands, the former reaching lemon size. The epitrochlear and axillary masses never drained spontaneously, nor were they sur-

#### Case XLII

Mrs. W. H., age 48, assisted Mrs. M. H. (Case XLI) in dressing rabbits at the C. market. A third woman (Mrs. C. H.) who helped dress these rabbits was taken acutely ill at the same time as Mrs. M. H. and Mrs. W. H., and after two weeks of identical ill-



FIG. 17. Mr. A. W. E., case XVII. Axillary adenopathy, with diffuse pyoderma. Six weeks after onset.

gically incised. She felt very weak until during the spring and summer of 1924 and was unable to return to her work until the fall.

Serum of Mrs. M. H., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

ness, died. Mrs. W. H. does not remember any scratch or cut on her hands. The day before Thanksgiving, 1923, she felt that she was "coming down with grippe," because of a severe headache and aching sensations in the back and extremities. She noticed on that day a papule on the tip of the middle finger of the right hand as well as epi-

trochlear adenitis which soon reached lemon size, and an English walnut size mass in the right axilla. She suffered from high fever, transient delirium, chills and sweats for ten days. She lost an indeterminate amount of body weight. The axillary mass was surgically drained the day before Christmas, 1923. She was unable to do any work until the following March. She states that she has never been entirely well since this illness.

Serum of Mrs. W. H., collected on March 1, 1928, was found by Francis to aggluti-

Henderson drained the axillary masses surgically about two weeks after they first appeared. Dr. Henderson told him at that time that he had the disease known to market men as "rabbit fever." Even though he worked through his period of illness, he felt very weak for several months. He has been in good health ever since.

Serum of Mr. J. collected on February 13, 1928, was found by Francis to completely agglutinate *Bacterium tularense* in a dilution of 1:80 and to partially agglutinate the organism at 1:160.



FIG. 18. Mr. F. C., case XVIII. Healing ulcer of fourth finger of right hand. Nine weeks after onset.

nate *Bacterium tularense* in all dilutions to 1:80.

#### Case XLIII

Mr. O. J., age 30, dressed rabbits at the E. F. market, just before Thanksgiving, 1924. He cut the little finger of the left hand, just above the nail, with a sharp rabbit bone. One week later, four masses appeared in the left axilla, each of walnut size. He suffered from high fever, chills and sweats. The lesions of the hand and axilla took three months to heal. Dr. O. C.

#### Case XLIV

Mrs. G. DeB., age 38, helped clean and dress rabbits at the C. market on the Saturday before Thanksgiving, 1924. She scratched the left thumb with a sharp fragment of rabbit bone. On the following Wednesday she became acutely ill with "grippe-like" symptoms. A lemon size mass developed in the left epitrochlear region and an orange size mass in the left axilla. Just above the bend of the left elbow a walnut size nodule developed. She applied poult-

tices to the epitrochlear mass and on the week before Easter, 1925, it drained spontaneously. One week after the epitrochlear drainage the axillary mass was surgically incised and about one-half pint of thick yellowish material escaped. During these five months Mrs. DeB. was unable to do her usual amount of work and it was only after the abscesses were drained that she began to feel better.

Serum of Mrs. DeB., collected on March 13, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

#### Case XLV

Mr. J. H. K., age 54, cut his right thumb accidentally with a knife while dressing rabbits on the eighth day of November, 1925, at the F. market, of Dayton. Four days after the injury, he complained of pain in the thumb, became very weak, developed a high fever, with chills and sweats and body aches. The ulcer which developed was incised and cauterized two days later. Four days after the pain developed in the thumb he complained of painful swellings in the right axilla. These rapidly fused and assumed grapefruit size. Two weeks later, when fluctuation developed, the glands were incised and drained by Dr. Damon Crist. The material which escaped on the initial drainage was thin and watery, but rapidly became very thick. During the first few weeks of his illness he lost considerable weight. The ulcer continued to give considerable pain and it was several months before it was completely healed. The axillary drainage continued for several weeks. He was unable to elevate his arm for many months. Mr. K. did not return to his work until May of 1926. The patient states that he has never felt well since the onset of his illness. Examination by the writer on January 27, 1928, showed an atrophic depressed scar of the ulcer 6 m.m. in diameter. In the right axilla was an atrophic linear scar healed by first intention, 3 cm. in length; there was no palpable axillary lymphadenopathy.

Serum of Mr. K. collected on January

27, 1928, agglutinated *Bacterium tularensis* in all dilutions to 1:160 (Francis).

#### Case XLVI

Mr. J. G. S., age 36; butcher. While dressing rabbits on November 25, 1926, he accidentally cut his hand with a rabbit bone. On the next day his arm became painful and a tender swelling developed in the axilla. He developed a high fever with repeated chills and sweats and remained in bed for one week. He was not seen by a physician until one week after the onset of his illness, when he was found to have a temperature of 101.8°F. There was found a small abrasion on the dorsal surface between the middle finger and the ring finger of the right hand. It had an indurated border with a small central deep ulcer, with a necrotic base. The right axillary lymphnodes were swollen to the size of a hen's egg. The right epitrochlear lymphnodes were of cherry size and very painful. At this time he had 12,800 white blood cells per cm. with 60 per cent polymorphonuclear neutrophils, 35 per cent small lymphocytes and 5 per cent large lymphocytes. The axillary mass became fluctuant and was surgically drained. Smears were negative for tubercle bacilli.

Mr. S. S., age 50, a brother of Mr. J. G. S., likewise a butcher, dressed rabbits at the same time. He cut the right index finger, with a rabbit bone, on November 20, 1926. The finger lesion did not heal. Five days later an ascending nodular lymphangitis developed together with axillary and epitrochlear lymphadenitis. He developed high fever, repeated chills and sweats, was greatly prostrated and lost considerable weight. His fever persisted until the day of his death, December 15, 1926. His death certificate was signed, "rabbit bone infection," by Dr. R. D. Potts.

Serum of Mr. J. G. S. collected on January 20, 1928, was found by Francis to agglutinate *Bacterium tularensis* completely in all dilutions to 1:160 and partially in 1:320 dilution. Similar results were obtained by Berry, at the Ohio Department of Health Laboratories.

*Case XLVII*

Mr. C. R. age 39; butcher. On the 16th of November, 1926, while cleaning rabbits at the O'B. market, Mr. R. cut the little finger of the left hand over the proximal interphalangeal articulation with a rabbit bone. He put iodine on the cut immediately. Five

The next day after the mass appeared at the left elbow he noticed a painful swelling in the left axilla. The axillary mass assumed walnut size, while the mass in the anticubital fossa reached orange size. Four days after the onset of his illness he noticed a mass in the right axilla which



FIG. 19. Mr. F. C., case XVIII. Epitrochlear adenopathy. No axillary adenopathy. Nine weeks after onset.

days later the finger gave him considerable pain in the morning. In the afternoon, he noticed a painful swelling at the left elbow. During the next 4 hours he developed a fever of 103.6°F. Because of financial difficulties, he remained at work even though he suffered from severe chills and sweats, splitting headache and severe body aches.

reached orange size in three days. The day following the appearance of the right axillary mass a similar swelling appeared in the right anticubital fossa, which reached orange size. The mass in the right axilla and right anticubital fossa were incised ten times and drainage continued for six months. During this six months's period he felt very

weak, was forced to lie down immediately after finishing his work, and did not commence to regain his lost weight until the following April. He is now (February 7, 1928) in excellent health.

Serum of Mr. R., collected on February 7, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:80.

#### Case XLVIII

Mrs. M. M., age 66; housewife. It was on Mrs. M.'s farm that J.S., C.D.M., A.W. E., and F. C. (cases XV to XIX) dressed the 500 rabbits purchased in Kentucky, just before Thanksgiving of this year. For many years she has assisted her son, C.D.M., in dressing rabbits which he has brought from Kentucky. On the night before Thanksgiving, 1926, while helping C.D.M. dress rabbits she cut the fourth finger of the right hand with a sharp rabbit bone fragment. In two days she became very sick and called in a physician who pronounced it "old-time bone-breaking grippe." An ulcer remained on the finger at the site of the inoculation for many weeks and a large right axillary mass appeared. On the day after Thanksgiving she developed a high fever, chills and sweats, severe headache, transient periods of delirium, and severe body aches. She was forced to remain in bed for seven weeks. She would try to get up and would discover that she was too weak, and would return to her bed. She claims that she has never felt well since this illness. A small deep scar of the ulcer still remains.

Serum of Mrs. M. M., collected on February 2, 1928, was found by Francis to agglutinate *Bacterium tularensis* in all dilutions to 1:320.

#### SUMMARY AND CONCLUSIONS

1. The discovery of forty-nine cases of tularemia in Dayton, Ohio, in the short period of four months, leads to the inevitable conclusion that tularemia is a common disease.

2. The most rapidly fatal case of tularemia of which there is any record

(4 days, 7 hours) provided an opportunity to study the early gross and histopathological lesions.

3. Twenty-four cases occurred during November, 1927, and in all but five instances were due to contact with Kentucky rabbits. In five cases, the disease occurred as the result of the handling of rabbits killed in the woods near Dayton.

4. A thorough investigation of the incidence of this disease in Dayton prior to 1927, led to the discovery of 25 cases, dating back to 1908. All but 2 of these older cases occurred in market men. At least seven deaths, attributable directly to tularemia, have occurred in Dayton during the past decade.

5. In forty cases in the Dayton series, the disease was of the ulceroglandular type. Sporotrichosis-like nodular lymphangitis was present in 6 patients. In 9 cases, there was no primary ulcer, the organism having apparently passed through unbroken skin (glandular type). No example of the oculoglandular or typhoid types were encountered.

6. In every instance, the disease resulted from direct contact with the wild cottontail rabbit. East of the Mississippi River, the deer-fly and wood-tick do not play any important rôle as transmitters of the disease.

7. Up to May 1, 1928, reports of 613 authentic cases, including the series here reported, have come to the attention of Francis. Cases have been reported in every state of the Union, except the New England States, Delaware, Wisconsin, and Washington.





FIG. 20. Mr. A. L. G., case XXI. Right axillary adenopathy. Seven weeks after onset.

There have been 23 recorded deaths (3.7 per cent). With the exception of 3 cases occurring among laboratorians in England, and 7 in Japan, all of the cases have occurred in the United States.

8. The organism was recovered directly from human tissues in two cases. A human serum modification of Francis' cystine glucose meat infusion peptone agar was employed.

9. It was demonstrated experimentally that the organism will pass through the unbroken skin. The organism retains its virulence in guinea pig splenic tissue, preserved in glycerine in an ice-box, for two months.

10. The diseases known to ophthalmologists as Parinaud's disease and *conjunctivitis necroticans infectiosa* are clinically similar to *conjunctivitis tularensis*.

11. The diagnosis is usually simple if one has a suggestive history, together with an influenza-like onset (fever, chills and sweats, severe headache and aching sensations in the back and extremities, marked prostration) and the characteristic primary lesion

and regional adenopathy. Confirmation is best obtained by specific agglutination tests at some laboratory provided with *Bacterium tularensis* antigen. Material from the primary lesion or regional lymphnodes may be injected into a guinea pig or rabbit, and the organism recovered on special cystine-containing media.

12. There is no specific treatment. The treatment is essentially symptomatic. The primary lesion is a granuloma, and incision is distinctly contraindicated. Surgical drainage of the involved lymphnodes is indicated only when definite evidence of suppuration is present. The effect of immune serum on the course of the disease will be the subject of a further report.

#### NOTE:

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## Editorial

### JOHN HUNTER, THE NATURALIST SURGEON

1728-1928

#### *His Influence Upon Internal Medicine.*

In the two hundred years that have passed since the birth of John Hunter the development of Medicine has reached such a stage in its evolution that the influence of this interesting individual upon that development can be more clearly seen and evaluated. He is ranked among the master minds of medicine. His name is linked with Harvey among the anatomists, and with Lister among the surgeons; and there is not a single field of practical medicine or surgery in which his name may not be mentioned as a great fore-runner. Yet, curiously enough, the reader of his life and works cannot confess to any feeling of attraction towards his personality—quite the opposite state is aroused. As a boy in the village of Long Calderwood near Glasgow his reactions were not regarded as becoming a Scots boy whose father came from an ancient line of gentry and whose brothers were preparing for careers in law and medicine. He was stupid in learning to read, idle and a cry-baby, a failure in the Latin School in which his brothers had been successful, and mother-spoiled. Surely today he would be rated very low in any intelligence test, and would be regarded with sus-

picion as to his future mental development. Even his relatives had no illusions as to his being a difficult child; but in their unprejudiced descriptions of him they mention several characteristics of saving-grace quality that serve to lessen the unpleasant impression his boyhood and early youth make upon us.

Although obstinate and rebellious as to book-learning, he was conceded to be observant, quick of perception and exceedingly neat of hand, particularly in anything of a mechanical nature. His own version of these unpleasant youthful years was "They wanted to make an old woman out of me, or that I should stuff Latin and Greek at the University; but these schemes I cracked like so many vermin as they came before me." Different indeed was he from his older and more attractive brother William, who also achieved lasting fame as a master in medicine. But the secret of John Hunter's apparent failure as a proper kind of a Scots boy was, as in the case of many another boy of many different periods in the world's history, that his heart's interest was *scientific*. He was born a *naturalist*, and a *naturalist* he remained all his days, and what he contributed to medicine and surgery was the result solely of this character of his intellectual make-up. He tells us later in his life, that as a boy he had the urge for an understanding of the natural world

about him, "the clouds, grasses, leaves, ants, birds, tadpoles and caddis-worms." He watched these and questioned people concerning them to no satisfaction. Books and book-learning he hated; to go bird's-nesting, to compare their eggs and note their differences in color, size and shape gave him his kind of mental satisfaction and discipline. It was but natural, therefore, that anatomy should attract him as he came to manhood's realization that there was work to be done in this world. So in September, 1748, he began work with his brother William in London, chiefly in the dissecting room, and in the second year became demonstrator to the students attending his brother's courses of lectures. John's life at this time showed that any charge of laziness made against him in early life was untrue, he slaved from morning to night in the most unpleasant business of the dissecting room of that period and its necessary relations with the resurrection men with whom he is said to have made great friends. Quite naturally the social amenities of such a life did little towards making a gentleman out of him, although his brother was given credit for making him a man. But circumstances brought him into contact with Cheselden during the summers of 1749 and 1750, and in the next year with Percivall Pott. From the former surely some refining influences must have touched Hunter, for Cheselden was noted for his refinement of manner and his love of art. Hunter's interest in pictures and prints in later life may possibly date back to his asso-

ciation with Cheselden. Nevertheless, Hunter's attitude towards the world, and particularly that of his own profession, savored of a contemptuous superiority; his conceit made him at times a most unlikable person, coarse and repulsive. If ever a human being was sold, body and soul, absolutely to his work that individual was John Hunter. His brother William was like him in this respect. Together they tore through life with untiring passion for scientific work, without other recreations or hobbies, putting only such value on the pecuniary rewards of practice as would enable them to obtain means whereby they could pursue their scientific passions. The results of this passion appear as an everlasting memorial in their individual and combined anatomical achievements. But the glory of all this accomplishment is tarnished by the controversies which the Hunter brothers carried out with the Monroes and Percivall Pott, and finally with each other, as was inevitable because of their natures. Work was the only bond between them; they would fight side by side against any outside claimant to their discoveries, and finally against each other when both claimed priority. All of this makes a sad story of the unpleasant aspects of human actions, even when viewed in the light of the controversial fashion of the times. The final estrangement of the brothers was their dispute over the discovery of the structure of the placenta and its communication with the uterus. No justifiable excuse or apology for their ugly quar-

rel has ever been shown, and the knowledge of it completely effaces any personal feeling of liking or admiration the reader of today might otherwise have incited within him by their other great qualities.

But it is neither a history of their lives and achievements nor an estimate of their personalities that I wish to present here. Rather is this brief sketch designed to illuminate the influence that John Hunter's life and works exerted upon the development of medicine. That this influence was a tremendous one is universally conceded. We give him a position among the masters—the great masters—of medicine. As a philosopher he has even been compared with Shakespeare. He is perhaps most commonly thought of by the medical profession as a great surgeon, and was called by Abernethy the master-surgeon of all times. Yet an operating-surgeon he surely was not. Few operations are ascribed to him; and the only important one associated with his name is the tying of the femoral artery for popliteal aneurism which had not previously been done. This operation was approached by him, not from the operative standpoint, but from that of anatomy, physiology and pathology. Hunter himself had no high opinion of operative surgery; he considered an operation to be a reflection on the healing art and an acknowledgment of the insufficiency of surgery. In truth, as far as surgery is concerned, Hunter was a surgical-pathologist—a biological philosopher. His interest lay in the anatomico-physiological principles involved in any morbid condition rather than in the

operative attack. The leading surgical consultant of his time, it is not known to what extent he operated upon the patients who came to him, or had others operate for him. He, himself, had a very definite dislike for the practical application of scientific knowledge. Practice was subordinate to anatomy and pathology. All that he received in fees he spent on scientific investigations and on his museum. The oft-quoted remark about that "damned guinea," reluctantly earned, only because he must have it to spend on his science, reveals the absorbing passion of his life. Even at the last, when his practice had become lucrative, he spent all on his work and left only his museum consisting of more than 13,000 specimens, for the support of his wife and children. The popular opinion of Hunter at the height of his fame is also revealing; he was regarded as a surgeon who would do everything to discover the nature of one's ailment, help it if it could be helped, but if not amenable to treatment, would do everything in the world to secure an autopsy on the patient. His museum or "Natural History" as he called it, was open to visitors two months in the year, October for the profession, May for "noblemen and gentlemen who were only in town during the spring." In every field of natural history, anatomy, physiology, pathology, anthropology, botany and geology he made discoveries of great importance and established new facts. For forty-five years of his life (1748-1793) he was engaged in "dogging the footsteps of Nature day by day" in order to spy out her secrets and to obtain for his mu-

seum any specimen that would throw light on the manner in which Nature defended living matter and repaired defects in living tissues. This was perhaps the keynote to his medical philosophy. He has often been called a "vitalistic" surgeon; he replaced the old surgical quackery and empiricism by the scientific method of observation and experiment. He was the first surgeon to make the actions and reactions of living tissues the foundation stone on which all surgical practice must be based. He was the first man of medicine to realize the unity of all living matter, and to assert that the study of the minutest forms of life would illuminate the more complex structures and functions of the human organism. Without the knowledge of the laws and conditions under which vital actions and reactions were originated and maintained the surgeon and the physician were pure opportunists, empirics or quacks. Hunter created thus a new epoch of medical philosophy; he laid the corner-stone of modern medicine. He saw clearly that disease was only altered life; he saw further that Nature attempted to return to normal life by resisting the causes of disease and repairing the damages resulting therefrom. He believed that all living matter possessed the power of defense and repair. Upon this he based his conception of the treatment and cure of disease; through observation he thought it possible to obtain a knowledge of natural defense and repair, and to apply these principles in the treatment of patients. This thought animated his entire life work, and was

responsible for his collection of ten or more thousand specimens that to him threw light upon these natural laws in the multiform methods of Nature. In this museum he attempted to collect everything that would throw light upon the laws of growth and repair. Without knowing anything of the histological changes underlying inflammation, he regarded its varied manifestations as essentially curative in nature, and his recognition of this fact constitutes perhaps his most important contribution to the practical side of medicine. He was more than a century ahead of his times in this conception, as well as in many another one. If we read Hunter today with the modern understanding, and substitute the modern terminology of reflex, functional adaptation, hormone-reactions, toxic effects, anabolic, katabolic, etc., for his *consciousness*," *sympathies*," *morbid poisons*," *combination*," *decomposition*," etc., we will be startled at their extremely modern quality. None of the discoveries in medicine made since his day puts him behind the times, for no matter what their interpretation may be at any period, the vital phenomena he saw and described will remain essentially the same. If we read Hunter's works with this spirit of insight we shall find that his observations threw new light on practically every organ and tissue of the animal organism. Our knowledge in many ways remains today where Hunter left it.

Hunter was not a scholar of his times; he knew no mathematics, no logic and was ignorant of the classics. How much better it would have been

for him and the world if he had added such erudition to his great store of intrinsic mental ability and energy. He was always handicapped by an inability to express his thoughts, and his written works suffered from this educational deficiency. He was born a genius possessing wonderful powers of observation, abstraction and analysis, and these qualities added to his insatiable love for work, his passion for original research, his indomitable will and his tremendous capacity for thinking made of Hunter the great philosopher of life and nature. He combined in an extraordinary degree the two philosophic methods of induction and deduction. In pathology particularly he employed the deductive method, reasoning from premises and hypotheses invented by himself. In spite of some errors the wonder is that so many of his speculative conclusions in physiology and pathology, made without the aid of microscope or chemistry, have been confirmed by later workers possessing this equipment. In deduction he often anticipated discoveries far beyond the facts at hand. Many examples of perfect induction are also found in his writings, but also others of fallacious reasoning by analogy and comparison. He used the inductive method chiefly in collecting and assembling the scattered facts of comparative anatomy and physiology, but much of his pathology was also based on induction. He employed the two methods, Deduction and Induction, at will, sometimes without fully coordinating the two methods,

but this was only because, as has been expressed by Morris, that he, in spite of his wonderful genius, "fell short of being an absolute monarch of the whole kingdom of the intellect." Hunter has been criticized because of certain obscurities; Buckle explains these by saying that the conflict in Hunter's mind between Deduction and Induction darkened his understanding. Otteley laid them to deficient education. Morris explains Hunter's obscurities by the complexity of the subject or the fact that Hunter's own mind was in doubt. Be this as it may Hunter was stated by Buckle to have "remodelled the fabric of Knowledge;" he is placed with Harvey, Bacon and Newton as a man of science, and with Shakespeare as a man of natural genius. His contemporary and critic, Jesse Foot, however, asked scornfully: "What was John Hunter's service to Medicine and Surgery?" Arthur Keith has probably given the best answer to this question: "If I had to inscribe the tag attached to the coat lapel of the shade of John Hunter as it applied for entrance to the Valhalla of the great medical dead, I would write: 'This is the man who discovered that every measure to further healing and to preserve health and life must be based on an accurate knowledge of the vital processes of living flesh'." For this reason Hunter revolutionized medicine, and he did it as a philosopher of abnormal life—in other words as a pathologist and not as a practitioner.



## Abstracts

*Experimental Tularemia in Birds.* By R. G. Green and E. M. Wade (Proc. Soc. f. Exper. Biol. and Med., May, 1928, Vol. XXV, No. 8, p. 637).

These investigators have previously reported that grouse are susceptible to experimental tularemia. Inoculation of an abrasion through the skin of a ruffed grouse results in a fatal septicemia. Preliminary experiments carried out on the susceptibility of the Hungarian partridge to experimental tularemia indicate that this bird is highly susceptible to the disease, a fatal infection resulting from an open inoculation of a skin abrasion. The pigeon appears to be relatively more resistant. In this bird an intramuscular injection causes the formation of a local lesion, and in some cases is followed by a generalized invasion by the organism. Even with the production of a septicemia, no clinical symptoms were observed in the pigeons in their series and those not killed have recovered. The ring-necked pheasant also appears to be relatively resistant to experimental tularemia. The domestic chicken appears to be absolutely resistant to the disease. Organisms injected intra-muscularly do not appear to invade and produce a general infection.

*A New Liver Function Test.* By Alice R. Bernheim (Proc. Soc. f. Exper. Biol. and Med., May, 1928, Vol. XXV, No. 8, p. 675).

A rise of the icterus index had been noted to occur following the intravenous injection of phenoltetrachlorophthalein. When bromsulphalein was used no rise in the index took place. At first the rise in index following the use of the phenoltetrachlorophthalein was thought to be its toxic action upon the liver. It was suggested by Dr. S. M. Bassett that, inasmuch as distilled water was used to dilute a 5 per cent to a

1 per cent solution in the case of phenoltetrachlorophthalein and no dilution was made in the case of bromsulphalein, the increase in icterus index might be due to the laking of red cells by the distilled water. Accordingly, injections of distilled water up to 100 cc. were given intravenously, and, as surmised, a rise in the icterus index was produced. From this observation the idea arose that this use of distilled water might serve as a liver function test. If the normal liver removes bilirubin from the blood, the source of bilirubin being the hemoglobin from destroyed red blood cells, it is reasonable to suppose that a disordered liver will remove it less efficiently. If, then in the normal person, after the injection of distilled water the icterus index rises from 2 to 4 points one-half hour after injection, with an average rise of 2.5 points and returns to its basal value in 5 hours, a greater increase in icterus index might conceivably be expected in the individual with a disordered liver, or the return to normal might be prolonged. Adequate dosage of the water was ascertained by experiment to be 25 cc. for individuals weighing from 100-110 pounds, with an increase of 5 cc. for every pound of body weight up to a maximum dosage of 50 cc. In the normal person results were obtained as stated. But contrary to expectations the injection of the water in abnormal cases occasioned either no rise in the index or a fall, according to the amount of dysfunction. The interpretation of these observations is at present wholly speculative. It seems unlikely that a disordered liver can more readily remove the bilirubin from the blood than a normal one. The results indicate that the test may be a measure of the bilirubin-forming, rather than of the bilirubin-removing function of the liver. Observations were carried out on 15 normal persons and on 112 hospital patients. The normal individuals

showed a rise of from 2 to 4 points in the icterus index. Of the hospital cases 28 showed either no rise or a fall. These 28 cases comprised: 5 of catarrhal jaundice, 1 of arsenical poisoning with jaundice, 2 of metastatic carcinoma of liver from primary in stomach, 5 of hepatic cirrhosis, 1 of cyst of liver, 1 of Wilson's disease, 1 of small liver with right lobe absent, 3 of carcinoma of head of pancreas, 3 of cardiac disease with decompensation, 4 of Hodgkin's disease, 2 of Graves' disease. The remaining 94 cases showed a rise in the icterus index. In 5 of these the diagnosis of liver disease was made: 2 cases with the clinical diagnosis of cirrhosis with ascites, 2 cases of enlarged liver in syphilitic patients, 1 case of localized carcinoma of liver, extension from gall bladder. Among these some indexes rose less than 2 points. Cases with the severest liver damage showed a fall in index, those with less damage showed no rise, and normal cases showed a rise of from 2 to 4 points. These facts make it seem possible that in some of the hospital cases showing a rise in index of less than the normal 2 points a corresponding slight liver dysfunction may be indicated. In 3 cases of thyroid disease (1 adenoma with symptoms of intoxication and 3 of Graves' disease) changes in the icterus index following the injection of distilled water corresponded to the rate of basal metabolism and the condition of the patient, the higher the metabolic rate, the lower the index. Bromsulphalein tests were made to check the water test. Where findings were normal in the dye test they were likewise normal in the water test. With the bromsulphalein test in jaundice there is always a 100 per cent retention of the dye one-half hour after injection irrespective of the severity of the liver involvement. With the water test the index either does not change or decreases according to the extent of damage. This test is accordingly a more delicate gauge of disturbance than the dye test, when jaundice is present. There is a fairly common impression that the intravenous injection of distilled water may produce unpleasant consequences varying from a mild chill to death. In none of these cases were there any un-

pleasant reactions. On the contrary restless patients were quieted, and all without exception experienced a feeling of well-being lasting several hours.

*Effect of Liver Extract on Erythrocytes and Reticulocytes in Normal Individuals.*

By C. H. Watkins, R. Johnson and Hilding Berglund (Proc. Soc. Exper. Biol. and Med., May, 1928, Vol. XXV, No. 8, p. 720).

The effect of liver extract in pernicious anemia may be analyzed from the point of view of the immediate reaction, as well as of the sustained reaction. The immediate reaction includes among other things three distinct morphological features: the normoblastic response, the reticulocyte response and the liberation of the mature erythrocytes. It is a well-established fact that the bone marrow in pernicious anemia is hyperplastic and contains large numbers of erythrocytes in various stages of development. In other words, there appears to be a difficulty in the maturation of the erythrocytes necessary for their discharge from the marrow into the circulation. This faulty maturation is in character probably morphological rather than chemical, for the cells in the marrow are completely filled with hemoglobin and products of hemoglobin have been deposited in the various tissues. Thus the hemosiderosis, in the classical interpretation of pernicious anemia looked upon as a proof of the hemolytic character of the disease, might indicate a destruction of erythrocytes in the foci where they were formed before they were ever delivered into the circulating blood. When liver therapy is instituted, the bone marrow presumably is stimulated to mature and release the cells. A slight retardation in the maturation as compared with the discharge explains the three morphologic features of the immediate reaction. The effects of liver extract upon six normal individuals were studied for a period of ten days during which they were given 3 vials of liver extract (Lilly, 343) or the equivalent of 300 gm. of raw liver daily. Their erythrocyte counts were, between 4,500,000 and 5,800,000. Daily erythrocyte and reticulocyte counts

were obtained. That the results might be reduced to a common base line, the original erythrocyte count of each individual was called 100 per cent, and the subsequent increase or decrease in erythrocytes was calculated in terms of the per cent of the original value. In all cases but one there was a definite increase in erythrocytes at the 10th day. The percentage is an irregular curve up to the value of 120.7 per cent on the 10th day. The irregularity of the curve may be due to an attempt of the body to overcome the polycythemia. In clear contra-distinction to the occurrences in pernicious anemia no increase in the reticulocytes took place in the normal individuals, the percentage remaining between 0.0 and 2.0 per cent. There was no change in the leukocyte counts. The hemoglobin followed the red count, but probably not in full proportion to the increase in red cells. In all cases the individuals developed some symptoms of polycythemia vera; thus varying degrees of headaches, epistaxis, acrocyanosis and abdominal distress, were encountered. Attention is called to the immediate response in the normal individual as compared with the delayed discharge of mature red cells in pernicious anemia. If in pernicious anemia we base our comparison on the occurrence of increased number of normoblasts, the first signs of response to the liver come as early in one group as in the other. Thus the liver extract in normal individuals as in pernicious anemia brings about an immediate release of red blood cells into the circulating blood. In the normal individual the maturation of the cells is complete and the release rapid; in pernicious anemia the maturation is retarded, discharge of incompletely matured cells occurs and precedes the discharge of fully matured ones; the process as a whole is prolonged.

*Hemoglobin Construction within the Body as Influenced by Diet Factors. A Consideration of Anemia Problems.* By G. H. Whipple (Am. Jour. of Med. Sc., June, 1928, CLXXV, No. 6, p. 721).

Whipple is convinced that a wrong assumption has seriously hampered the study

of certain human anemias. Attention has been focussed upon hypothetical toxins which were supposed to destroy red cells *in vivo* and thus bring about the anemia. Because it can be demonstrated that a few types of anemia were due to toxic or parasitic destruction of red cells (septicemia, drugs, malaria) it has been assumed that all other forms of anemia must be due to some hemolytic toxin produced in the intestinal tract, kidneys, tumor growths, etc. This idea is given up with great difficulty. Pernicious anemia is the stronghold of those who believe in toxic red cell destruction as the essential etiologic factor. The anemia associated with bothriocephalus infections, which is often called pernicious anemia, has long been cited as the real proof of the toxic etiology of pernicious anemia. Meulengracht reviewing all of the known facts could find no direct evidence for any demonstrable toxic substance in the bothriocephalus anemias, although he concludes that pernicious anemia is due to an obscure intestinal intoxication. Nevertheless, each one of his deductions may be used as an argument in favor of the theory that pernicious anemia is a *deficiency* disease. Whipple in 1922 advanced the view that in pernicious anemia there is a *lack* of stroma building material but a great excess of pigment and pigment building material. The important observations of Minot and his collaborators may be interpreted as evidence in favor of a *lack* of a stroma-producing substance so that pernicious anemia may prove to be a *deficiency* disease. It is difficult to reconcile the prompt remission in pernicious anemia due to liver feeding with a causative agent in the form of an intestinal toxin. It will be profitable to reexamine all of the anemias and search for a possible deficiency factor rather than for an elusive toxin. It is permissible to assume that in the anemia of cancer cachexia we are dealing with a hemoglobin building material which is perhaps used up by the more vigorous and rapidly growing tumor cells. In the case of intestinal stricture or general malnutrition there may be a severe anemia due to lack of materials unabsorbed from the intestinal tract. The anemia of nephritis may

be explained as due to faulty conservation of hemoglobin building material. The normal kidney plays a part in the conservation of pigment material, and it may be assumed that the diseased kidneys fail in this function is in other excretory ones. It may be accepted as established that simple anemias due to loss of blood can best be treated by means of diet therapy. Pernicious anemia has been shown to be amenable to diet. Why not examine other obscure anemias and marrow diseases for a possible deficiency factor?

*The Blood Pressure in Pernicious Anemia.*

By J. Lerman and J. H. Means (Amer. Jour. Med. Sc., June, 1928, Vol. CLXXV, No. 6, p. 777).

It is generally recognized that blood pressure is low in pernicious anemia, but the literature contains no adequate statistical study of the subject. Text-book articles on pernicious anemia usually state that the pressure is "low" or "very low." The present study is based on the blood pressure findings in 500 consecutive cases of pernicious anemia from the Massachusetts General and Peter Bent Brigham Hospitals. The observations were all made with the patient in bed by the auscultatory method of Korotkoff. Analysis of the observations made showed only slight variations in the averages due to age or sex. Compared with

the average figures for normal people the blood pressure is significantly lower in pernicious anemia. The incidence of systolic hypotension in controls varied from two to three per cent, and of diastolic from 0.3 to 1.6 per cent. In the pernicious anemia series the incidence was about 11 per cent for systolic and about 30 per cent for diastolic hypotension. These percentages corrected for the age distributions of the controls are still higher. Hypotension is a more frequent condition in pernicious anemia than in tuberculosis. It appears that in pernicious anemia hypotension is associated with an almost complete disappearance of hypertension whereas in tuberculosis patients the existence of hypotension has but little effect on the frequency of hypertension. The infrequency of hypertension in pernicious anemia is of distinct interest, being practically as rare as is the presence of free hydrochloric acid in the gastric juice. Until further control data on the anemia have been secured no diagnostic weight can be laid on blood pressure. The pulse pressures in pernicious anemia are higher than the corresponding normal ones by 9 to 17 mm. of Hg. This increased pulse pressure is apparently a feature of an increased volume flow of blood of a compensatory nature, and finally results in hypertrophy of the cardiac musculature. With improvement in blood picture the pulse pressure tends to diminish.

## Reviews

*Clinical Laboratory Procedures.* By George L. Rhodenburg, M. D., Director of Laboratories, Lenox Hill Hospital; Consulting Pathologist, Lincoln Hospital, Misericordia Hospital, Beth David Hospital, New York. 266 pages. The MacMillan Company, New York, 1927. Price in Cloth, \$3.25.

This is a collection of laboratory methods which in the hands of the writer have shown their relative simplicity and clinical accuracy over a period of years of actual use. Where several methods are known or in common use, the one which practical experience has indicated, for one or another reason to be preferred, has been arbitrarily selected. Some knowledge of laboratory procedure on the part of those using the volume is pre-supposed. No claim is made for originality, and free use has been made of all current text-books. An effort has been made to present concisely such procedures as are frequently undertaken in routine work. No attempt has been made to discuss the value of a given procedure, or to furnish a bibliography. The volume bears out the modest statements of the preface. The most important and most frequently used laboratory procedures in clinical diagnosis are given in simple concise form and the whole represents a well-chosen collection. They are given in sufficient detail to be usable by the student or laboratory assistant who possesses ordinary laboratory initiative and experience. The book is interpagged with blank leaves for additional notes or new methods. It is a handy and convenient little manual for the clinical laboratory and will be found very useful there.

*The Examination of Patients.* By Nellis B. Foster, M. D., Associate Physician to the New York Hospital; Associate Professor of Medicine at Cornell University

College of Medicine. Second Edition, Revised. 392 pages, 83 figures, partly in color. W. B. Saunders Company, Philadelphia and London, 1928. Price in cloth, \$4.50.

The first edition printed in 1923 was reprinted in January and April, 1924, and in September, 1925. It was written in the belief that it would be of help to the practitioner of medicine, its aim being to present as clearly and concisely as possible the methods on which accurate diagnosis rests. The author's experience in hospital and private practice impressed him with the need for such a book as an intermediary between the classical descriptions of the text-books of medicine and the treatise on the latest modes of treatment. Refinement of diagnosis compels the use of the trained senses of touch, sight and hearing, but it is certain that the modern development of laboratory methods and the over-exploitation of the clinical laboratory have diverted attention from these most important fundamentals. While this fact may be realized by the physician whose professional activities are confined to hospitals, its realization is not general. Rarely does the laboratory test alone reveal the nature of disease; it is usually only a support to other evidence which must be obtained in other ways, from the clinical features chiefly. Clinical medicine rests upon accurate diagnosis. This fact is being recognized today as never before. The treatment of symptoms is, in any major sense, an aberration that has vanished. The ability to seize on the relevant facts out of a mass of data is the mark of the true clinician, and this applies both to the knowledge of pathological details and the clinical features. While the knowledge of the former has been extended in a marvelous degree, the clinical features, on which the differential diagnosis of one disease from another

depend, are relatively few in number. The first edition brought to the author many letters from physicians acknowledging the practical help derived from it and requesting that the subject of differential diagnosis be attempted in the same concise way as that employed in describing methods of examination. This the author has attempted in this book, with some misgivings on his part. The examination of the book shows, however, that these were not justified; and the reviewer regards this volume as one of the most useful that could be placed in the hands of the medical student or practitioner. It represents an exposition of the highest type of medical practice—technical proficiency, accuracy of observation, and knowledge in the assembling and interpretation of the data secured. Diagnosis is a science and an art; a science in the method of using facts secured, and an art largely in the mode of collecting the facts. There are many sources of error in diagnosis, such as errors of judgment, errors in analysis, errors in data, but the commonest of all are errors in technique. Technique in music produces beauty of tones; in medicine it secures accuracy of data. This book then is an argument for perfection of technique in diagnosis, and is such we recommend it in the highest terms of approval.

*Text-Book of Clinical Neurology.* By Israel S. Wechsler, M. D., Assistant Professor of Clinical Neurology. Columbia University, New York; Attending Neurologist, The Montefiore Hospital, New York. 725 pages, 127 illustrations, octavo volume, W. B. Saunders Company, Philadelphia and London, 1927. Cloth, \$7.00.

The object of the author has been to give a digest of what is known in neurology without stressing polemic material or detailing case reports. References to literature have been more or less consistently omitted from the text. The work is based mainly on personal teaching and clinical experience, and, therefore, represents in a great measure an individual approach to bedside neurology. The author hopes that the personal touch will make up for many

of its omissions and defects. For the benefit of those who would pursue the subject farther the author has given at the end of each chapter a few of the more useful references bearing on the topics discussed. In doing this he has made an effort to separate the wheat from the chaff. He has also departed from the customary practice of illustrating the text with numerous photographs of patients, and has relied more on reproductions of pathological specimens and anatomical drawings which permit of the interpretation of signs and symptoms and lend understanding to the clinical manifestations. As the book is essentially one of clinical neurology, he has attempted to present, wherever possible, the various diseases in such a way that the signs and symptoms grow out, as it were, of the anatomicopathological substratum and are seen to be consequent upon the underlying physiological disturbance. The anatomical and pathological facts on which the subsequent description of the clinical entity, its development and course is based, are outlined in brief, concise paragraphs. The author has also been wise in omitting the customary introductory chapters on anatomy and physiology, for unless they actually form part of each disease entity they have no place in a clinical neurology. No student expects to learn anatomy or physiology from a textbook of neurology. Of all the branches of medicine, clinical neurology lends itself best to the interpretation of signs and symptoms in terms of disease structure and function. The modern tendency in neurological diagnosis is to weave anatomy, physiology, pathology and symptomatology into one pattern. Because of the inevitable overlapping the classification of neurological diseases offers many difficulties, and it is difficult to be consistent in following either a pathological, anatomical or clinical classification. The author has adhered roughly to the nosology based on the last two, and has adopted the order followed by Oppenheim. The field of nervous disease has grown so vast that it is practically impossible, except in an encyclopedic work, to gather everything between the two covers of the volume. Wechsler has, therefore, omitted consider-

ation of most of the diseases of the ductless glands usually included under neurology, since they are more properly placed under general and experimental medicine. He discusses them only in so far as a given endocrine disturbance has any direct neurological implication. Part I consists of a very complete exposition of the "Method of Examination;" diseases of the spinal cord are discussed in Part II; the peripheral nerves in Part III; the brain in Part IV; and the neuroses in Part V. The various diseases of those structures are discussed in a clear and concise style, which tends to give them an individuality that is so often lacking in the text-book descriptions of diseases of the nervous system. For that reason this text-book should have an especial value for the medical student, who is, so often, discouraged by what seems to be hopeless confusion as far as the differentiation of nervous affections is concerned. Essential points of knowledge only are given, and unsettled matters are only very briefly discussed as to the main points in question. The illustrations serve their purpose very well. A large amount of good common sense is scattered through the pages of the book; and the paragraphs on treatment are unusually free from fads. Psycho-analysis is given no more than its proper consideration. On the whole this work has much to commend it as a text-book.

*The New York Academy of Medicine Lectures on Medicine and Surgery.* First Series, 1927, 319 pages, 39 illustrations. Paul Hoeber, Inc., New York, 1928. Price in cloth, \$5.00.

The first series of Practical Lectures for the general practitioner arranged by the Committee on Medical Education and given at the New York Academy of Medicine in 1925-27 met with such favor that the lectures are now published in book form in the belief that they will meet a need which is felt by the profession generally. The volume consists of fifteen lectures delivered by the following: Harlow Brooks, John F. Erdmann, John E. Jennings, S. J. Kopetzky, E. Libman, G. M. MacKee, J. A. Alexander, L. K.

Neff, J. O. Polak, H. Pool, David Riesman, M. G. Schlapp, J. M. Wheeler, H. B. Wilcox, and S. W. Wynne. In the order of lecturers named the subjects of the lectures were respectively, as follows: The Treatment of Cardiovascular Syphilis, Intestinal Obstruction, Surgical Aspects of Medical Conditions, Clinical Aspects of Common Otological Infections, General Infections by Bacteria, The Cutaneous Manifestations of Syphilis, Climate in Tuberculosis, Useful Drugs in Clinical Practice, Obstetrical Problems in General Practice, Surgical Aspects of Diseases of the Thyroid, The Treatment of Pneumonia, Pathological Causes of Human Misconduct, Remarks on Eye Conditions, Problems of the Child's First Year and Contagious Diseases. This group of interesting subjects receives individual and original treatment in the hands of these well-known medical writers. Brook's article on the treatment of cardiovascular syphilis in its therapeutic optimism will be of the greatest significance to the practitioner in the numerous suggestions contained within it. Erdmann's article on Intestinal Obstruction is of great practical value; the etiology and symptomatology are concisely given and the suggestions for treatment most sensible and practical. Likewise, the articles on the Surgical Aspects of Medical Conditions and the Clinical Aspects of Common Otological Infections contain many valuable hints and suggestions for the internist.

All the articles are all far superior to the average medical journal article. They have an individual and original point of view, based upon extensive or unusual clinical experiences, and contain much valuable clinical knowledge not to be found in any textbook. While the style of the different articles varies considerably they are all interestingly written, and such cannot be said of some of the volumes of lectures that it is now the fashion for hospitals and clinics to publish. This series, however, is of real practical value to the internist, and may be recommended for such, as collateral reading. The book is printed in the usual good style and manner characteristic of Hoeber productions. The illustrations, particularly those in McKee's article on the cutaneous manifestations of syphilis, are very good.

*Brain Abscess. Its Surgical Pathology and Operative Technic.* By Wells P. Eagleton, M.D., Newark, N. J. Medical Director, Newark Eye and Ear Infirmary, Newark, N. J.; Chief of the Division of Head Surgery, Newark City Hospital; Attending Craniologist, Newark Presbyterian Hospital; Consulting Craniologist, St. Barnabas Hospital and St. Michael's Hospital, Newark, N. J., Muhlenberg Hospital, Plainfield, N. J., Mountainside Hospital, Montclair, N. J.; Chief of the Section of Surgery of Head, Base Hospital, Camp Dix, N. J., 1917-18. 297 pages, 40 illustration. The MacMillan Company, New York, 1922. Price in cloth, \$7.00.

This monograph is the result of considerable intradural experience combined with animal experimentation and postmortem studies. Realizing that surgical as well as pathological and diagnostic information may be obtained from postmortems the author invariably made a personal effort to obtain an autopsy on all cerebral cases coming under his observation, and was fortunate in missing this in very few of the fatal cases previously examined or operated upon. Surgically considered intracerebral abscess stands in a class by itself, the problems presented in its surgical treatment differing from those of suppuration in other parts of the body and distinct from these encountered in the treatment of non-suppurative lesions of the brain. As many of the technical problems presented still remain far from solution the author calls attention to the unique physiological factors and pathological changes presented within the dura, and to the technique which in the author's opinion, most satisfactorily meets them. The success of intradural surgery always will depend upon utilizing every advantage offered by the preventive and reactive efforts of nature, while a single technical error may mean the loss of the patient's life, or at least of his subsequent usefulness. Cushing's technique has been largely used by the author in operating for intracranial suppuration. The writer attempts to correlate the surgical treatment of the different pathological lesions of brain abscess, since if even a moderate degree of success is to be achieved in the treatment of brain abscess, the surgical manipulation in each individual

case must be adapted to the exact pathological lesion present. With this object in view emphasis is laid upon the pathology and on mechanical changes and a classification is adopted which is capable of individual clinical recognition, because the author believes that our present knowledge should enable us not only confidently to diagnose the presence of brain abscess, but also in a large proportion of cases to determine its location and whether or not it is surrounded by a capsule. To accomplish this the surgeon must divest himself of certain ideas inherent in the old classification of aural and nasal origins, and must conceive of them not according to their immediate origin, but pathologically, according to the causative lesion of entrance into the central nervous system; that is, whether by extension by direct tissue suppuration or by retrograde thrombophlebitis, for which the author suggests the terms *Adjacent (Secondary)*, and *Intercurrent (Tertiary)*, when immediately occasioned by a secondary gross lesion such as sinus thrombosis, to differentiate both from abscesses originating from bacteria circulating free in the blood stream, the latter being pathologically *metastatic*, even though the original focus of infection may be in the ear or the nose. The author states that one of the chief objects of this work is to enable the surgeon to approach the treatment of brain abscess in a pathological as well as a technical mental attitude. The book has naturally a strong personal character, since it is largely an account of experience in more than fifty cases of adjacent brain abscess that have come under the writer's observation. The book was written because the author recognizes that many deaths might have been avoided had he earlier been in possession of the knowledge gained by his failures, and which he now offers here for the aid of others. Case histories are given in detail, and technique is minutely described. Altogether it is a very complete monograph upon the subject, and of great value from the diagnostic side, as well as from the operative. The case histories, in themselves, are most instructive. The abstracts of the reported cases of brain abscess given in the Appendices are also valuable in assisting the reader to the fullest possible grasp of this subject.



## College News Notes

### DR. SMITHIES HONORED BY THE BOARD OF GOVERNORS

The following is a resolution of the Board of Governors, adopted at their meeting on March 9, at the close of the Twelfth Annual Clinical Session:

"In recognition of the earnest, untiring, and faithful service of our retiring President, Frank Smithies, in the upbuilding and maintenance of The American College of Physicians, be it resolved that the Board of Governors accord to him its hearty vote of appreciation, thanks, and commendation. And be it further

"Resolved that this resolution be spread upon the Minutes of this meeting of the Board of Governors, and that a copy be sent to Dr. Smithies."

To all who are familiar with the history of the development of the College of Physicians the recognition of the part played by Dr. Smithies as expressed in the above resolution of the Board of Governors will seem but a slight acknowledgment of the great service rendered by the late President. Dr. Smithies rescued the College from an early death and through his great exertions saved the frail organization, and in the years that followed built it up into the successful institution that now without any doubt is destined to become a leading force in the growth and progress of internal medicine in the United States. This great work was accomplished in the face of the most bitter opposition and the early days of the College's growth were beset by many difficulties which were successfully surmounted through his

untiring zeal and tremendous efforts. That the College was actually created by him and made what it is today through his work must be acknowledged by those who follow him, and it is fitting that those who now take up the guidance of the policies of the College bear this fact in mind with gratitude and render him due credit for his great service. From him they can doubtless obtain most valuable advice in the consideration and settlement of the problems that must still be worked out in order to make of the College a more helpful instrument in the development of American Medicine. From all quarters Fellows of the College have expressed their desire that he will still continue to take an active interest in the affairs of the College.

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### DR. OTIS HONORED

Dr. Edward O. Otis, F. A. C. P., of Boston, was recently honored by a dinner of a large number of physicians and friends at the University Club. This celebration marked the completion of forty-two years of service by Dr. Otis on the staff of the Boston Dispensary, having been first appointed in 1886. He was presented with a humidor with an engraved silver plate. Dr. Otis who is now eighty years of age graduated from Harvard Medical School in 1877, and has received the degree of Doctor of Science from the University of New Hampshire and Tufts College. He did postgraduate work abroad, and has established an international reputation in the field of Tuberculosis. He is an ex-president of the National Tuberculosis Association and of the American Climatological and Clinical Association,

is a member of the American Public Health Association, the American Medical Association, and his county and state associations. He has served as a member of the Board of Governors of The American College of Physicians to represent his State for some years.

Col. Bailey K. Ashford, F. A. C. P., recently retired from active service in the Medical Corps of the United States Army and located in San Juan, Porto Rico, was recently appointed by the Government of Porto Rico as its representative to the International Congress on Tropical Medicine and Hygiene to be held at Cairo, Egypt.

Dr. Jonathan C. Meakins (Fellow), Montreal, was elected President of The American Society for Clinical Investigation at Washington, D. C. on April 30.

Dr. Kenneth M. Lynch (Fellow), Charleston, S. C., and Dr. Sidney K. Simon (Fellow), New Orleans, La., were elected Vice-Presidents of The American Society of Tropical Medical at Washington, D. C. on May 2.

#### DR. WARTHIN HONORED IN INDIANA UNIVERSITY

Dr. Aldred Scott Warthin, director of the department of pathology in the medical school of the University of Michigan, was awarded an honorary doctor of laws by Indiana University at commencement Monday, June 11, with the following citation:

"In recognition of your achievements as teacher, author, editor, physician, as director of the pathological laboratory at the University of Michigan for 25 years, and as an investigator in the field of pathology, on recommendation of the board of trustees, I take pleasure in conferring upon you, an alumnus of Indiana University, the degree of Doctor of Laws.

Dr. Bernard L. Wyatt, F. A. C. P., Medical Director of the Desert Sanatorium of Southern Arizona at Tucson, has been appointed Director of an Institute of Research to study the nature of solar radiations and their effects on living matter. The Board of Directors of the Desert Sanatorium has appropriated \$250,000.00 for this study.

Dr. Solomon Solis-Cohen, F. A. C. P., of Philadelphia, has been made the Medical Director of the Jewish Convalescent Home at Willow Grove, Pa.

Dr. Tom Bently Throckmorton (Fellow), of Des Moines, Iowa, was re-elected during May as Secretary of the Iowa State Medical Society.

Colonel Bailey K. Ashford (Fellow) after many years of distinguished service in the United States Army Medical Corps retired on February 11. From 1913 to time of retirement, he was President of the Board to Study Tropical Diseases, U. S. Army, and has been stationed in Porto Rico. Since 1925, he has been a member of the Committee on Tropical Research of the National Research Council, and since 1926, has had the appointment of Professor of Tropical Medicine and Mycology at the College of Physicians and Surgeons, Columbia University, New York City. He is a Fellow of the American Medical Association, an ex-President of the American Society of Parasitologists, an ex-President of the American Society of Tropical Medicine, a member of the Association of American Physicians, and a member of the Association of Military Surgeons of the United States.

Dr. Stuart Graves, F. A. C. P., now Dean of the University of Louisville, School of Medicine, has been appointed Dean of the School of Medicine of the University of Alabama, beginning with the fall semester, to succeed Dr. Clyde Brooks who will act as Chairman of a newly created Faculty Committee on Research. The School of Medicine of the University of Alabama is preparing a program for a four year medical course, and Dr. Graves, Dr. Samuel W. Welch, F. A. C. P., State Health Officer, and Dr. James S. McLester, F. A. C. P., Professor of Medicine, and President Denny of the University will constitute a special advisory council to consummate the plans for the course. An extensive study of the best medical schools and teaching hospitals will be made. The plan contemplates the appointment of full-time teachers in the major branches, establishment of a hospital, nurses training school, etc.

## OBITUARY

George Nicholas Acker, 2nd, M.D. (Associate, February 20, 1924; Died, February 27, 1928.)

Doctor Acker was born in Washington, D. C., August 2nd, 1888. After his attendance in preparatory school he entered Gettysburg College, Pennsylvania, from which institution he was graduated. Later he entered the medical department of the College of Physicians and Surgeons, Columbia University, New York City, from which institution he was graduated in 1914. After his graduation he did hospital work in New York City. He obtained his internship in St. Luke's Hospital in which institution he served from June 1914 to January 1916. In 1916 he received an appointment as resident physician in St. Luke's Hospital. Later he served as instructor in the Department of Clinical Medicine of his Alma Mater and was for a short time an assistant to Dr. Lambert.

At the outbreak of hostilities he entered the United States Army Medical Corps, serving for two years and four months, reaching the grade of Captain. He was a member of the Stewart Walcott Post of the American Legion, the Veterans of Foreign Wars, and the Military Order of the World War.

After the War he established himself in the City of Washington where his Uncle, the late George Nicholas Acker, Professor of Pediatrics at George Washington University Medical School, one of the early members of the American Pediatric Society, had long been established in practice. Doctor Acker not only was the namesake of his distinguished Uncle but he seemed early to exhibit many of the qualities shown in the long fruitful life of his Uncle.

In establishing himself in practice he was appointed an Associate in Medicine at George Washington University, being in charge of the Department of Physical Diagnosis. He was instructor in Clinical Medicine in this institution at the time of his death, which occurred February 27th, 1928.

Doctor Acker was a member of the American Medical Association, The Medical Society of the District of Columbia, The Med-

ical Society of the George Washington University, The Southern Medical Society, The Medical Society of Maryland, and The Medical Society of Virginia. He also held membership in the American College of Physicians and the Clinico-Pathological Society.

He was a member of the Garfield, Children's and Emergency Hospital Staffs.

Doctor Acker's inherent thoughtfulness and courtesy toward all, together with his skill as a physician, soon built for him a large clientele. It is to be regretted that such a promising professional career would be so abruptly ended. To quote from an obituary written by one of his intimate friends—"He bubbled with the sort of humor that chases gloom to its hiding place and leaves no wound. His wit was always kind. He refreshed the sick and weary soul like a Summer shower and hatred had no companionship with him."

At his death the profession lost a great physician—humanity a friend.

Doctor Acker was buried in Arlington National Cemetery.

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VTH INTERNATIONAL MEDICAL  
CONGRESS FOR INDUSTRIAL  
ACCIDENTS AND OCCUPA-  
TIONAL DISEASES,  
BUDAPEST, 1928

In accordance with a resolution of the "Permanent International Committee", the Vth International Medical Congress for Industrial Accidents and Occupational Diseases will be held in Budapest, Hungary, September 2nd to 8th, 1928.

All those who are engaged in the subjects to be discussed, are cordially invited to attend.

Budapest, 12th March 1928.

Prof. TIBERIUS GYORY

Under Secretary of State,

Chairman of the Organization Committee.

Prof. TIBERIUS VEREBELY

Professor at the Pazmany Peter University of Budapest, Chairman of the Executive Committee.



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